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Carbon microelectrodes with customized shapes for neurotransmitter detection: a review

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Abstract

Carbon is a popular electrode material for neurotransmitter detection due to its good electrochemical properties, high biocompatibility, and inert chemistry. Traditional carbon electrodes, such as carbon fibers, have smooth surfaces and fixed shapes. However, newer studies customize the shape and nanostructure the surface to enhance electrochemistry for different applications. In this review, we show how changing the structure of carbon electrodes with methods such as chemical vapor deposition (CVD), wet-etching, direct laser writing (DLW), and 3D printing leads to different electrochemical properties. The customized shapes include nanotips, complex 3D structures, porous structures, arrays, and flexible sensors with patterns. Nanostructuring enhances sensitivity and selectivity, depending on the carbon nanomaterial used. Carbon nanoparticle modifications enhance electron transfer kinetics and prevent fouling for neurochemicals that are easily polymerized. Porous electrodes trap analyte momentarily on the scale of an electrochemistry experiment, leading to thin layer electrochemical behavior that enhances secondary peaks from chemical reactions. Similar thin layer cell behavior is observed at cavity carbon nanopipette electrodes. Nanotip electrodes facilitate implantation closer to the synapse with reduced tissue damage. Carbon electrode arrays are used to measure from multiple neurotransmitter release sites simultaneously. Custom-shaped carbon electrodes are enabling new applications in neuroscience, such as distinguishing different catecholamines by secondary peaks, detection of vesicular release in single cells, and multi-region measurements *in vivo*.

Keywords

carbon nanomaterials; neurotransmitters; analytical chemistry; sensors; neuroscience; 3D printing

1. Introduction

For decades, carbon has been used as an electrode material because of its high conductivity, wide potential window, and relatively inert chemistry.[1,2] Traditional carbon materials, including glassy carbon and graphite, serve as electrodes in sensing, energy storage, and super capacitors.[3] Carbon-fiber microelectrodes (CFMEs) are a fundamental tool for

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neurotransmitter detection with a micron-scale diameter.[4] The graphitic electrode surface has defect sites which promote biomolecule adsorption but it is relatively smooth, and the geometry is limited to cylinders or disks.[5,6] Nanomaterials are often added to carbon electrodes because of their large surface-to-volume ratio, increased interfacial adsorption, and rapid electron transfer kinetics.[3,7] Another goal of bioanalytical studies is a smaller electrode size for precise localization and less damage to the tissue, and thus many studies are aimed at making nanoscale carbon electrodes.[8] Changing the size or shape of the electrode, on either the macro- or nanoscale, will influence its electrochemical properties and enhance its use in different applications.

The nanostructure of carbon electrodes is being explored to achieve high selectivity, trapping, implantability, and multifunctionality. Carbon nanomaterials, including carbon nanotubes (CNTs),[9–12] carbon nanospikes (CNSs),[13–15] and nanodiamonds (NDs)[16,17] provide electrodes with rougher surfaces or porous structures. CNT fibrils also trap analytes on the time scale of rapid electrochemistry, leading to thin-layer electrochemistry and enhanced selectivity of neurotransmitters.[10,18,19] Carbon nanoparticle modifications improve the electrochemistry of carbon fibers. They increase sensitivity by enhancing electron transfer kinetics and prevent fouling for neurochemicals that are easily polymerized.[5,20,21] The coating also increases the active surface area and the number of adsorption sites on the electrode to favor neurotransmitter detection.

There are also emerging methods to customize the whole geometry of the carbon electrode and not just change the nanostructure. Nanopipettes are pulled from glass or quartz capillaries and have either a cavity or an open tip at the nano-sized sharp end.[22,23] Cavity nanopipette electrodes are nanoelectrodes with trapping effects. Porous carbon films are formed via drop-casting or dip-coating a specific carbon material on the substrate to increase the electroactive area. The pyrolysis of polyimide films using a laser is another strategy to generate porous graphitic carbon structures.[15,21,24–27] New methods are also being developed to customize carbon electrodes into complex shapes beyond disks and cylinders. 3D-printed carbon electrodes have customizable shapes with nanoscale features, and are batch fabricated with high reproducibility.[28–31] Carbon microelectrode arrays contain multiple microelectrodes in different shapes, such as pillars,[32,33] needles,[2,34–37] spikes,[13,14] or bands made of CNTs,[38,39] carbon nanofibers,[40–42] or amorphous carbon.[43–45] The arrays have a high surface-to-volume ratio and an adjustable density. The goal is to use these complex structures for multi-analyte measurements and to target selective detection of certain neurotransmitters by changing electrochemical properties.

In addition, these different microelectrode designs aim to improve the performance for different applications. For example, nanosized electrodes provided better spatial resolution for single-cell measurement and vesicle characterization.[46] Carbon microelectrode arrays were applied for simultaneous detection at different sites *in vivo*.[47] Diamond microelectrodes were also useful for *in vivo* studies because of their anti-fouling properties.[48] Porous carbon materials, such as 3D graphene foams, were used as skeletons for cell culture and as sensors with electrochemical techniques.[49]

In this review, we survey different types of carbon-based electrodes and examine how studies to change the electrode shape affect electrochemistry. We emphasize studies that use novel approaches to achieve complex geometries and highlight surface structures that are rationally designed to enable new electrochemistry. These techniques are broadly relevant, and applications are highlighted mainly in neuroscience and bioanalysis. While previous reviews detailed the structure and chemical properties of carbon nanomaterials, here we concentrate on how nanomaterials enable unique shapes and the electrochemical properties that result from those shapes. Controlling the nanostructure and the macrostructure of the electrode is useful for applications including *in vivo* measurements, single cell measurements, and vesicle impact electrochemical cytometry (VIEC). These studies show that focusing on the electrode geometry enhances electrochemical properties and will lead to better electrodes for neurochemical applications.

2. Customized shapes of carbon electrodes

2.1 Carbon electrodes with nanostructuring

Classic carbon electrodes used for neurochemistry include glassy carbon (GC), graphite, and carbon fibers (CFs).[50–52,1,3,53–55] However, the performance of CFs and graphite is improved by changing the nanostructure to add edge planes and defect sites, which favors the adsorption of biomolecules.[2,13,56] Cathodic arc deposition is a physical vapor deposition technique that uses a high current, low voltage arc to deposit thin, hard films and nanocomposites, such as diamond-like carbon (DLC) films and tetrahedral amorphous carbon (ta-C). However, cathodic arc deposition is costly and requires high energy.

Many graphene-like nanomaterials are made via chemical vapor deposition (CVD) (Table 1).[40,42,57–59] Improvements in CVD have been made to allow longer and more aligned nanomaterials. Water vapor assisted cleaning to remove amorphous carbon during deposition facilitates growth of longer CNT that are further fabricated into CNT fibrils or CNT yarns.[57] Catalyst free methods are better than those using a catalyst, which must be removed. Plasma-enhanced CVD (PECVD) allows catalyst-free synthesis of vertically aligned CNTs and carbon nanospikes.[13,14] Liquid injection chemical vapor deposition (LICVD) is catalyst free and pumps in a metallocene-hydrocarbon solution during synthesis, enabling large-scale vertically aligned CNT production with high purity. Many electrodes are based on nanomaterials made with these advanced CVD methods because the long and aligned CNTs facilitate fabricating porous electrodes with trapping properties. For electrodes, predictable structure and properties are important, so robust and reproducible fabrication is required.

There are two methods for making nanostructured carbon electrodes: (1) coating nanomaterials on (2) an electrode or growing nanomaterials on a substrate. Coating nanomaterials, performed via drop-casting, dip-coating or electrodeposition, is quick and easy but the deposition is more difficult to control. CFMEs modified with nanodiamonds and nanohorns via drop casting showed good sensitivity for dopamine detection, but coverage was not always uniform.[17,60] A comparison of drop-casting, dip coating, and electrodeposition shows electrodeposition is the best coating method because the voltage provides more reproducibility.[61] The second method for producing nanostructured electrodes is to grow the nanomaterial directly on metal or semiconductor substrates to

make microelectrodes. For example, PECVD growth of CNSs on metal substrates leads to electrodes with a controllable coating depending on time in the PECVD chamber.[13–15] Growth of nanomaterials is advantageous because the structure can be tuned by the growth conditions. Figure 1 shows different carbon materials with nanostructures that were applied to neurotransmitter sensing, including MWCNTs, nanodiamonds, graphene foam and nanospikes. The following sections will highlight how using different growth techniques results in different electrode shapes and different electrochemical properties.

2.2 Porous carbon-based electrodes with trapping properties

One advantage of many carbon nanomaterial electrodes is that the materials are porous, which leads a large surface roughness and restricted diffusion, trapping molecules near the surface. In this section we show how many carbon nanomaterial electrodes have thin-layer electrochemistry,[71] a unique mass transport process where diffusion layer is so small it is neglected. Typical thin layer cells have a long electrode with a wall close to it that traps a small volume near the electrode, with only a small pore for fluid entry. Hubbard and Anson developed a thin layer cell with a centimeter electrode and a cavity 1 to 10 μm wide,[72,73] and found voltammograms dramatically different than diffusion controlled voltammograms. For an ideal reversible Nernstian reaction, the CV shapes are symmetrical instead of a typical “duck shape” and the potential difference between the anodic and cathodic peaks is 0 V.[72,74] Similarly, for FSCV measurements using trapping electrodes, the length of the cell also needs to be about a hundred times longer than the pore size; the structures with nanomaterials have long cavities compared to the small diameter of the entrance pores. The pores in between the CNTs or nanomaterial on a rough surface lead to thousands of thin layer cells on the surface.[18,75–77] If the roughness of the electrode surface is large enough that the crevices are deeper than the diffusion layer thickness, then molecules are trapped on the time scale of a fast electrochemical experiment.[18] For example, the diffusion layer thickness for dopamine is approximately 0.9 μm for one FSCV cycle; thus trapping occurs in cavities over 1 μm.[10] In FSCV, the CVs for thin layer electrochemistry have similar cathodic and anodic peak currents, similar to slow scan CVs, although kinetics are too slow to have a ΔEp of 0 V.

Many different strategies have been developed to fabricate porous electrodes and here we show that disparate types of electrodes with trapping effects have similar electrochemistry. Figure 2 shows example trapping electrodes, including CNT-based and nanopipette electrodes. Many of the trapping electrodes contain long CNTs that are synthesized on a flat substrate to guarantee a large surface roughness. CNT yarns are made by twisting CNT fibrils into a long thread;[57,78] thus, they have a porous structure after they are polished to a disk electrode (Figure 2A). A taI palm carbon nanosheet with a highly porous surface structure had a large surface area and pore-size distribution that led to better electrocatalytic properties for high sensitivity dopamine and uric acid detection.[79] Another study used a composite of MWCNT/ta-C to fabricate a porous film (Figure 2B), which trapped dopamine and increased anti-fouling properties in biological media.[80] Laser-induced scribing of polyimide films produces a porous graphitic surface, and these electrodes have enhanced electron transfer kinetics due to the large specific area of the extended 3D porous network. MWCNT arrays (Figure 2C) and cavity-carbon nanopipettes (Figure

2D) also have thin-layer electrochemistry even though they are very different types of electrodes.[10,19] Fig. 2E shows example electrochemical behavior of these structures. The ΔE_p of the cyclic voltammograms of long MWCNT arrays dramatically decreases with increasing scan rate, because trapping is enhanced in faster experiments (Figure 2E).[77,81] When surface roughness is larger than the diffusion layer thickness, the concentration of analytes within the porous structure is larger, the redox current is higher, and the CV shapes are more symmetrical with a smaller peak-to-peak separation.[82] Thus, these studies show that a wide variety of carbon materials lead to similar thin layer electrochemistry with rapid electrochemical techniques.

Simulations and theory were developed to understand how nanostructuring leads to thin layer electrochemistry. Kant proposed a model to describe the electric double layer dynamics of a porous electrodes with amperometry and electrochemical impedance spectroscopy.[75,83,84] This model will be useful in the future to explain how diffusion dynamics are influenced by electrode geometry, shape, and size. Recent work comparing experiments and COMSOL simulations shows when the surface roughness of the electrode is comparable to the diffusion layer thickness, thin-layer diffusion dominates at high scan rates, while planar diffusion dominates with slow scans.[18] The cyclic voltammograms switched from a “duck shape” characteristic of diffusion to a more symmetrical shape signaling thin layer electrochemistry (Figure 2F). These were the first theoretical studies to show how the trapping effect occurs with nanomaterials and why it is more obvious with FSCV measurements. This modeling work is the first for FSCV and will provide a theoretical framework to predict properties of trapping electrodes.

Porous nanomaterial electrodes have other special electrochemical properties beyond the shapes of the CVs that make them useful in rapid neurotransmitter analysis.[85] For neurotransmitter detection at CNT yarn electrodes, the signal drops less with increasing FSCV repetition frequency; thus, there is higher sensitivity and a higher temporal resolution. Porous carbon electrodes with trapping effects are beneficial in neurochemical detection because they enable a higher repetition frequency without losing sensitivity.[10] The oxidation currents for neurotransmitters are enhanced due to the continuous redox cycling within the thin layers. Nevertheless, it also leads to a slower time response because molecules are restricted from diffusing in and out of the pores; however, the time delay is negligible during the measurement. Thin-layer electrochemistry is also used to differentiate neurochemicals with similar CV signals by enhancing side reactions.[10,18] For quasi- or irreversible redox reactions, the secondary reaction products are trapped and currents enhanced in the cyclic voltammograms, especially for higher repetition frequencies in FSCV.[10] Epinephrine has the highest secondary oxidation peak, which enables differentiation from dopamine and norepinephrine (Figure 2G).[10] Thus, trapping leads to unique electrochemical properties that enhance temporal resolution and selectivity.

2.3 Polymer-based electrodes and flexible electrodes.

One simple method to nanostructure a carbon surface is to use conductive or charged polymers. Polypyrrole (PPy), poly(3,4-ethylenedioxythiophene) (PEDOT), and polyaniline (PANI) are the most common polymers.[83,86] PEDOT has similar electronic properties to

metals and is positively charged, while Nafion is a negatively charged polymer that is applied to carbon electrode fabrication to prevent fouling of neurotransmitters, such as serotonin and histamine.[87–89] Carbon nanomaterials, such as CNTs, cab ne immobilized in polymers to enlarge the surface area and the advantages are low-cost, biocompatibility, and flexibility.[43,90] Polymers are also functionalized to enhance chemical properties in a variety of applications. Carbon fibers with polytannic acid (PTA)-doped nanoporous conductive polyaniline have nanoporous structures and biofouling resistance due to the polymer.[86] A similar antifouling effect was observed at silica nanoporous membrane (SNM) modified CFMEs, which prevents the biomolecules from attaching to the surface while still preserving the permeability to oxygen.[91] One disadvantage of carbon electrodes with polymer coatings is a slower time response due to diffusion in the film. However, they have enhanced electroactive area that enables sensing with a higher sensitivity.

Polymers are also used as the electrode body to fabricate flexible electrodes. Polyimide (PI), polydimethylsiloxane (PDMS), and parylene C are commercially available, low-cost, and chemically inert. PI films have a long history as an implantable material, a high heat and chemical resistance, and wide applications in electronics. PI is a high carbon-content polymer and is carbonized to graphitic material via laser or focused ion beam, allowing custom shapes by tailoring printing designs to the application. Both laser-induced graphene (LIG) from PI and polyethersulfone (PES) had excellent electrochemical properties and conductivity, but PI-LIG exhibits a higher sensitivity, whereas PES-LIG has an enhanced performance for side reactions due to sulfur substitutions.[92] Custom laser printed electrodes from PI will see more use in the future because they are flexible electrodes that are less likely to damage the brain tissue.

PEDOT, PDMS, and silicone are flexible substrates that are modified with carbon materials.[87,93,94] For example, a hybridized composite of PEDOT and graphene oxide coating enables implantation of a gold microelectrode and shows good durability and performance in PC12 neural cell tests.[95] PEDOT/MWCNT composite films have good flexibility, biocompatibility, and excellent electrochemical performance at the neural interface.[9] Polymer-based carbon electrodes have a wide range of applications in electrochemical sensing because the electrode surface is easily functionalized to favor biomolecule detection by adding surface functional groups, such as amine groups and carboxylate groups.[96] Conductive or charge-selective polymers enable high selectivity to neurotransmitters with good antifouling properties. The large surface area of carbon composites provides high sensitivity during measurements.

2.4 Nanopipettes and nanosized electrodes

The majority of carbon electrodes in electrochemical analysis are several microns wide and are unable to measure in neuronal synapses, which are typically 0.02 micron wide; thus, a reduction of size is useful for neural studies. [30,97] Nanoelectrodes cause minimal tissue damage, probe a local cellular environment, and have enhanced electrochemistry. The ultra-small scale leads to less charging current, enhanced radial diffusion, and a high current density at the electrode surface. Because noise is proportional to background current, signal to noise ratios are good for nanoelectrodes even though absolute currents are small.

Nanopipettes are a multifunctional tool in analytical chemistry and electrochemistry that are applied in sensing, sequencing, delivery, and imaging. The nanopipette openings are approximately 30-60 nm for quartz and 150-200 nm for borosilicate glass. Carbon is deposited on the inside of the nanopipettes and one advantage of CVD fabrication is that conditions are adjustable to control the thickness, to make either a solid tip or an open pipette.[23] The electrochemical performance of the nanopipettes is different than macroelectrodes. Solid tipped CNPEs have small signals due to small surface areas, but are useful for detection in small organisms, such as the *Drosophila*.[22] Cavity-nanopipettes (CNPEs, Fig. 2D) trapped molecules at the tip and yielded a higher sensitivity with exhaustive redox cycling.[10] Cavity carbon nanopipettes have been applied to vesicle counting and sizing in a living cell with vesicle impact electrochemical cytometry (VIEC).[98] By controlling the size of the open tip, the kinetics of vesicle release during exocytosis was determined. Other studies with nanopipettes examined vesicle release kinetics in cell-to-cell communication and measured vesicle contents *in situ* in live cells.[46,98,99] Nanopipettes are manufactured in bulk with a reproducible shape, but are also fragile and tips can be easily broken.

Nanoelectrodes are also made with other methods, which take advantage of the high sensitivity of nanomaterials and new nanoprinting techniques. Flame-etching produces carbon-fiber nanoelectrodes small enough to be inserted in synapses (Figure 3A) or be used intracellularly to study single cell exocytosis via intracellular VIEC.[99,100] The wet etching method is more controllable and dipping a cylindrical CFME into a concentrated KOH solution while applying 7 V (Figure 3B) leads to a nano-scale sharp tip that enables the vesicle cargo discrimination.[101] Coating a thin layer of carbon nanospikes on niobium metal wires, which have submicron-sized tips (Figure 3C), also leads to rigid, robust nanoelectrodes that are not easily broken.[15] Because of their extremely small size, nanoelectrodes exhibit a highly efficient diffusional mass transport with spherical diffusion at the edge; therefore, the current density is high. Carbon-based nanoelectrodes have various designs based on fabrication methods, including disk shape, needle shape, and cavity shape,[23] which function differently in analytical studies. The nano-size causes minimal tissue damage, and enables exploring small organisms and synapses.

2.5 3D printed carbon electrodes

3D printing, a special direct laser writing (DLW) technique, is one of the most powerful techniques to design and construct complex shapes with high reproducibility.[102] Printed, polymeric 3D structures are pyrolyzed to carbon that has a similar structure to glassy carbon.[28,29,103] During thermal annealing, the carbon structure shrinks in size but the design is maintained.[29,30] Direct laser writing was first designed to write patterns of metals for electronic devices, but now has extensive applications in fabricating microfluidic devices and carbon electrodes.[26,102] For electrode fabrication, DLW, with two-photon adsorption, polymerizes the photosensitive material to create three-dimensional shapes. The 100 nm resolution of DLW is independent of diffraction limit, so it is able to create nano-scale features in a precisely controlled manner. Unlike traditional photolithography, DLW does not require layer-by-layer fabrication or coating but it focuses a laser beam on an interior spot of a transparent material, which absorbs photons to polymerize and construct complex

structures. DLW enables the fabrication of tailored complex structures directly from a digital file; thus it guarantees consistency in constructing a large number of samples.

3D printing with nanolithography has the potential to revolutionize electrode design because of the vast designs that can be printed. Fig. 4A shows examples of 3D printing to develop carbon electrodes with custom shapes (Figure 4A) and nano-sized carbon electrodes (Figure 4B). [29,30] The pyrolyzed carbon from 3D printing has a high D/G ratio with a defect-rich surface structure, which enhances the electron transfer at the interface. 3D-printed electrodes are robust and reliable for detecting dopamine *in vitro* and in tissue. However, designs must be optimized because a shadow is created underneath the printing substrate when the substrate is blocking the laser from the top. Thus, it is important to consider the substrate size and focusing position during printing. The size of the 3D printed nanoelectrodes is smaller than the resolution of the printer because the micron-sized features shrink 3 to 6-fold when pyrolyzed. The tips are insulated in nanometer thickness aluminum oxide and then cut with a focused ion beam to expose a nano-sized disk.[30] The 3D printing method enables batch fabrication and 3D printed electrodes were applied to measure acetylcholine-stimulated dopamine in the adult fly brain. 3D printing techniques are also used to fabricate carbon microarrays or electrodes with customizable shapes for biological studies. For example, a printed nanoneedle can be used for synapse or single cell measurements.[15,104] A fused deposition modeling 3D printing technique was used to manufacture 3D carbon electrodes from polylactic acid and carbon black composite with ideal electrochemical performance; however, it was challenging to reduce the size of the carbon electrode with this type of printing.[105] 3D printing coupled with pyrolysis is a novel technique to generate carbon-based structures' however, designs and printing strategies are still under development.

Laser-induced graphene (LIG) is three-dimensional graphene that is carbonized from polymers by CO_2 laser scribing with customizable patterns. Recently LIG was used in flexible carbon-based sensors[106,107] as LIG was patterned in a polyimide film (Figure 4C).[108] DLW was used to carbonize polyimide films to construct a non-enzymatic carbon electrode that was used for hydrogen peroxide detection.[109] Three-dimensional LIG with grass structures had good selectivity in the detection of multiple neurotransmitters because of its large surface area and porous structure leads to many adsorption sites.[110] DLW is a powerful and novel tool to construct nano-sized structures, and it is highly reproducible for batch fabrication.

DLW and 3D printing enable the construction of carbon electrodes with dense nanostructures on the surface; thus, they have other applications in energy storage, such as developing supercapacitors and batteries, which are not considered in this review.[103,111–113] The disadvantage of DLW is that it is relatively slow and requires expensive instrumentation due to the highly precise focusing optics and beam control system. The advantage is truly customizable shapes and nano-sized features which cannot be fabricated by traditional methods.

2.7 Carbon-based microelectrode arrays

Currently, most carbon electrodes, including CFMEs, are single entities that only sample from a single region. Microelectrode arrays (MEA) are an ideal tool to overcome issues with spatial resolution by measuring from multiple areas. MEAs have a high surface-to-volume ratio, high current density, and reduced ohmic drop compared to macroelectrodes due to needle or spike-like nanoarrays.[76,115] Metal MEAs are widely used in microelectronic devices but they do not have good biocompatibility for tissue applications, while carbon-based MEAs are more biocompatible and electrochemically active. Screen-printed arrays were initially used but they have a relatively low resolution.[24,35,116] Newer fabrication methods allow custom configuration of the array to achieve different electrochemical applications.[117] MEAs with multiple microelectrodes and large electroactive sites have applications in neuroscience both *in vivo* and *in vitro*, including recording network firing in rat brain slices, deep brain stimulation, and synaptic remodeling.[67,94,117,118] The development of microelectromechanical systems (MEMS) facilitates the recording of electrochemical signals at multi-region and multi-channel simultaneously.

One method to make MEAs is using multiple carbon fibers. A multi-channel intraneural carbon fiber microelectrode array (CFMA) of 16 fibers was used to record physiological action potentials from small autonomic nerves. They successfully recorded vagal nerve activity and monitored firing rate changes in breathing and blood glucose in rat brains.[119] A scalable carbon fiber micro-wire style array was fabricated on a silicon wafer for neural recording with 32 microelectrodes, the highest density of all micro-wire style carbon arrays to date.[120] Carbon-fiber electrode arrays have many potential applications, such as neural recording, biosensing, and nerve stimulation.[117,120–123]

Direct growth of nanomaterials via CVD is another strategy for vertically aligned MEA fabrication. Carbon materials, including MWCNTs, CNFs, and BDD, are synthesized with different sizes and lengths during a controllable deposition process. MWCNTs are the most common carbon material for MEAs because of their high density of states, large surface area, and good electron transfer kinetics. Within a vertically aligned MWCNT forest, the mass transfer shows thin layer diffusion with increasing scan rates.[81] CNTs with a tube-shape structure were applied in CNT-based electrode arrays.[94,124] A three-dimensional carbon nanotube with was designed on-chip with a well-defined geometry and the application was anchoring to form neuronal networks for physiological studies.[118] MWCNT microelectrode arrays with isolated MWCNT islands had good biocompatibility and could be implanted for up to three days.[125] Arrays will facilitate multisite measurements and multiplexed operations, which have traditionally been difficult for *in vivo* neurotransmitter measurements.

3. Applications

3.1 Distinguishing different analytes

3.2.1 Dopamine determination in the presence of interferents—Dopamine is an important neurotransmitter involved in motor and cognitive functions and deficits in dopamine are implicated in Parkinson’s disease symptoms. Measurements of dopamine

in the brain are complicated due to the interference of other electroactive compounds. Ascorbic acid (AA) and uric acid (UA) are common antioxidants with similar oxidation potentials to dopamine, and are present at extracellular concentrations several orders of magnitude higher than dopamine in the brain.[69,126,127] The dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) is present in high concentrations, and has a similar structure and electrochemical signature to dopamine.[128–130] Thus, the selective dopamine determination of dopamine in the presence of other interferences is vital in carbon electrode development. Designs that enable dopamine discrimination are summarized in Table 2.

CNT yarn microelectrodes were developed for dopamine determination in the presence of DOPAC and AA with FSCV (Fig. 5A).[19] The trapping effect from the micron-scale crevices enhances secondary oxidation reactions, leading to better selectivity. By manipulating repetition frequency and pH, dopamine was determined with FSCV by its secondary peaks, in the presence of AA and DOPAC.

Carbon-based composite electrodes are used for selective dopamine determination by adjusting the composition. Reduced graphene oxide-bimetallic PdAu nanocomposites enable the simultaneous determination of ascorbic acid, dopamine, uric acid, and rutin.[131] Both CV and differential pulse voltammetry (DPV) show distinct and well-separated oxidation peaks for different analytes. A polyvinylpyrrolidone (PVP)-graphene composite sensor is used to detect ascorbic acid, dopamine, and uric acid.[132] The PVP-graphene composite has increased stability and dispersion compared to pure graphene and high electrocatalytic activity. A three-dimensional nitrogen-doped graphene generates multi-dimensional electron transfer pathways and improved electrocatalytic activities for simultaneous detection of AA, UA, dopamine, and acetaminophen.[133] A modified glassy carbon with poly(β-cyclodextrin)/carbon quantum dot or poly(glycine)/graphene oxide was developed for co-detection of dopamine with other neurotransmitters and amino acids by hydrophobic and hydrogen bonding interactions.[134,135] Carbon composite electrodes have a large surface area, abundant active sites, and functional groups that enhance dopamine detection or increase the signal difference for cations for selective measurements.

3.2.2 Discrimination of different catecholamines—Dopamine, norepinephrine and epinephrine are the main catecholamines, with different functions in the brain, but their structures differ only by 1 functional group, so the main oxidation peaks appear at 0.6 V for all of them.[8,136] Trapping electrodes, such as CNT yarn microelectrodes and cavity nanopipette electrodes, boost selective detection of catecholamines with FSCV based on thin-layer electrochemistry.[10] Catecholamine molecules undergo a quasi-reversible redox reaction mechanism, and the oxidant quinone molecules are either reduced or cyclized via intra-molecular Michael addition to corresponding leuco-chromes (Fig. 2G).[137] The catecholamine-chrome molecules are further oxidized to generate a secondary oxidation peak on the cyclic voltammogram.[138] The trapping electrodes enhance the secondary peak currents of epinephrine, which cyclizes the easiest as a secondary amine, and all three catecholamine compounds are discriminated based only on CVs. However, trapping electrodes are not as good for neurotransmitter quantitation, so computational techniques are needed, such as machine learning and principal component analysis.

3.2.3 Selective detection of other neurotransmitters and neurochemicals—

Serotonin (5-hydroxytryptamine) is a neurotransmitter that regulates mood and sleep. The oxidation potential of serotonin is similar to dopamine and CFMEs are more sensitive to serotonin than dopamine.[139,140] However, the detection of serotonin is complex because it polymerizes easily and causes electrode fouling, so antifouling properties are needed.[141] Carbon nanotube-fiber electrodes with abundant defect sites reduce chemical fouling by serotonin as well as biofouling.[142] CNT yarn microelectrodes are also resistant to surface fouling and have a high temporal resolution for serotonin detection.[66] Nanopalladium decorated multi-walled carbon nanotubes (PdNP:MWCNT) enable serotonin determination in biological fluids.[143] In many studies, carbon composite electrodes with large surface areas are used to discriminate serotonin from other neurotransmitters. A cyclodextrin (CD)-functionalized carbon composite favors the discrimination of serotonin and dopamine based on the host-guest recognition.[144] These studies improve serotonin detection mainly by nanostructuring to increase sensing area, but other strategies for more specific analyte enhancement could be developed. The abundant active sites on carbon composites in the porous structure could be functionalized with oxide groups and carboxylate groups, which facilitate neurotransmitter adsorption.

Hydrogen peroxide is a reactive oxygen species in the body, and also a byproduct of many oxidase enzymes, such as glucose oxidase, glutamate oxidase, and cholesterol oxidase.[145] Hydrogen peroxide requires a relatively high potential for oxidation (>1 V), near the FSCV switching potential.[2,146,147] Platinum electrodes are widely used for H_2O_2 electrochemical oxidation due to their fast electrode kinetics and catalytic effects; however, Pt electrodes easily biofoul and are expensive.[145,148] Carbon, as a versatile and inexpensive electrode material, needs to be functionalized in order to decrease the overpotential and increase electron transfer kinetics. Nanoporous carbon-fiber microelectrodes using heat-treatment were developed to improve the catalytic performance for hydrogen peroxide detection.[149] Other designs include a carbon-nanotube modified, laser-induced graphene electrode[150] and a nanobiocomposite using MWCNTs and reduced graphene oxide nanoribbons for enzymatic biosensing of hydrogen peroxide.[151] Similarly, reduced graphene oxide was combined with silver nanoparticles for hydrogen peroxide sensing with enhanced electron transfer rate.[152] These novel electrode designs with varying shapes and structures maintain a good stability and electrochemical performance, and could be used as the basis for peroxide based biosensors in the future.

Future studies could discriminate neurochemicals with high oxidation potentials, such as histamine, adenosine, and ATP. For example, histamine is another neurotransmitter that polymerizes easily and fouls the electrode.[89] Adenosine and ATP have similar oxidation potentials as hydrogen peroxide; thus, the main oxidation peaks of these compounds are similar.[153] However, adenosine and ATP have distinct secondary oxidation peaks at a lower potential that help distinguish them. One strategy to enhance ATP detection is adding amine groups or metal nanoparticles o the surface.[96,154] Table 2 lists strategies for detection of these compounds for neurochemical applications.

3.3 Single cell measurements

Electrochemical detection is useful for single cell measurements, as the electrodes are placed on or inside a cell to quantitate exocytosis using single cell amperometry (SCA). Recently, single cell measurements were enhanced by shrinking the electrode to hundreds of nanometers, allowing better characterization of specific release locations or implantation into a cell to measure intracellular vesicles. For example, a nano/micro-tip electrodes was used to characterize the role of DJ-1 protein on vesicular catecholamine release via SCA, proving that knocking out the DJ-1 protein significantly prolonged the exocytosis events.[167] A cavity nanopipette combined with resistive pulse measurements was used to simultaneously quantify the content of catecholamine and the size of vesicles intracellularly.[168] Flame-etched, carbon-fiber nanotip electrodes enable intracellular VIEC, revealing a high fraction of serotonin release in human gut cells (Figure 5B).[100] Figure 5C shows the amperometric recording of nanoscale vesicles individually in the cell cytoplasm with wet etched CFMEs.[101] Nanoelectrode amperometry is providing insight into diseases, such as the quantitation of dopamine release inside a dopaminergic synapse, finding that harpagide increases and restores dopamine release in a Parkinson disease model.[169] The good spatial and temporal resolution of nanoelectrode amperometry will provide more fundamental understandings on synaptic neurotransmitter release. The shape of the electrode has an effect on the amperometric measurements, with nanotip microelectrodes providing faster and higher responses for single cell measurement than traditional disk electrodes. Open carbon nanopipettes (CNPs) were also applied in single cell measurement to count molecules and determine release kinetics of vesicular release.[98] The radius of the pipette influences the sensitivity and the kinetics response, while the size of the vesicle also determines release kinetics of vesicular transmitters. Using nanoITIES and scanning electrochemical microscopy (SECM), acetylcholine release in a single synapse was quantified.[170] SECM provides high spatial resolution for nanotip positioning, and nanoscale electroanalytical methods will help characterize the mechanisms of synaptic neurotransmission in the future. However, the instrumental requirements of the expensive microscope still limit its applications. The small size of nanoelectrodes prevents damage of the cell, but also limits the sensitivity, which makes nanoelectrodes difficult to apply in tissue measurements. Therefore, future applications will include surface treatment or fabricate new types of robust nanoelectrodes to improve the nanoelectrode performance.

3.4 Multi-channel and multi-region measurements

Single microelectrode detection in the brain is the current standard, but it provides limited spatial resolution. Implanting multiple electrodes provides enhanced spatial resolution. The simplest examples implant two separate electrodes. For example, electrodes implanted in different hemispheres of the brain proved that there is coordination of dopamine transients across hemispheres.[47] However, two electrodes implanted in the hippocampus brain slice proved spontaneous adenosine transients were not coordinated and happened randomly.[171] Arrays are required to understand coordination of neurochemistry signals across the brain. Two different enzyme coated CFMEs for glucose and lactate were used to determine stimulated dopamine release increases striatal lactate availability.[172] Therefore, multiple channel FSCV enables studies of interactions of neurotransmitters at multiple sites in tissue.

For more channels, microelectrode arrays (MEAs) with multiple channels are being developed.[40,113] For example, reduced graphene oxide nanocomposites on MEAs were used to monitor dopamine release under deep brain stimulation in rat (Figure 5D).[165] A 7-channel MEA combined with amperometry enabled multiple measurements of vesicular release in a single cell, showing that release is not the same all over a cell.[173] In the brain, an MEA made of 16 microelectrodes was used to simultaneously monitor neurotransmitter the heterogeneous spatiotemporal dynamics of neurotransmission.[39,174] Chronically-implanted electrode arrays were developed to monitor dopamine long term in primates, where animals must be used for long term experiments and stable detection is needed for months.[175,176] Coating PEDOT on CFME arrays improves the chronic implantation recording signals.[177] MEAs currently provide multiple detection sites for the same neurotransmitter with simultaneous measurements, but also could be modified to detect multiple neurotransmitters simultaneously. However, the main limitations are the difficult fabrication techniques, the overall size of the arrays, and data analysis development needed for *in vivo* applications.

3.5 In vivo studies

Carbon-fiber microelectrodes are widely used in animal studies due to fast time response and biocompatibility, however, the performance can still be optimized. For example, the carbon surface structure can be modified to improve the antifouling properties for *in vivo* studies. Nanoporous membranes significantly block the surface fouling for *in vivo* detection. For example, an electro-grafted silica nanoporous membrane-coated CFME was used for *in vivo* oxygen measurement in the rat brain.[86,91] Polymers change the shape of the electrode and also the chemical properties to alleviate fouling. Diamond is another carbon-based electrode that has good antifouling properties due to the hydrophobicity of the diamond structure and multiple channel boron-doped polycrystalline diamond (BDD) microelectrodes are good for in vivo dopamine monitoring.[64] A diamond microelectrode was useful for monitoring phasic reward in monkey brain via voltammetry, and anti-fouling properties enabled longer implantation times.[178] The sp^3 diamond structure and the hydrophobicity of diamond reduces the protein adsorption on the electrode surface, which makes the diamond electrode anti-fouling.

Several approaches to carbon-based nanoelectrode fabrication were developed recently for *in vivo* applications. For example, 3D-printed carbon nanoelectrodes enable region-specific dopamine release *in vivo* in adult fly brain.[30] A glutamate biosensor was fabricated via coating enzymes on carbon nanoelectrodes to measure glutamate release in cells and *in vivo*.[179] Nano-sized biosensors will cause less damage for *in vivo* measurement; moreover, nano-sized glutamate sensors will also be useful for single cell detection to investigate glutamate release mechanisms. Nanoelectrodes have the potential to approach the synapse or localize in very discrete brain regions. However, the applications for *in vivo* measurements are still limited because of the decreased sensitivity with smaller size, so nanostructuring is needed to increase the activity of the surface while maintaining a small size.

3.6 Beyond neurochemistry

Carbon microelectrodes are important for neurotransmitter monitoring, but their applications are not limited to neurochemical detection. For example, carbon microelectrodes are also

sensitive for metal ion measurements.[180] Heavy metal ions including Cd^{2+}, Pb^{2+}, and Cu^{2+} are selectively detected via carbon microelectrode arrays with 1 μg/L limit of detection.[181] A carbon-based ion-selective electrode enabled anodic stripping voltammetry for metal ion detection. In addition, coating electrodes with ion selective membranes further enhances metal detection.[182] CNT microelectrodes are also applied for heavy metal ion detection in tap water.[183] The large surface area and fast electron transfer are especially important for metal sensor design.

Custom shaped carbon electrodes are also used for other applications. For liposome electroanalysis, CFMEs and nanopore microelectrodes facilitate liposome content analysis in real time (Figure 5E).[166,184,185] Liposome electroanalysis provides a better understanding of the effects of cell membranes on exocytosis, and it is also a good platform for ultramicroelectrode or nanoelectrodes characterization. In addition, modified carbon microelectrodes are also applied in capacitor fabrication.[186–188] For example, vertically aligned graphene thin-film electrodes shows good performance for on-chip microsupercapaitors.[113] Integration of VS_2 nanosheets into carbon also shows high energy density.[189] In these applications, tuning the shape affects sensitivity and electron transfer kinetics which will improve electron performance.

Carbon microelectrodes are also used for scanning microscopy applications for fundamental research. Scanning ion conductance microscopy (SICM), scanning electrochemical microscopy (SECM), and scanning electrochemical cell microscopy (SECCM) are used for high resolution electrochemical mapping. For example, SICM was used to investigate the surface charge effects on electroosmotic flow delivery from a nanopipette.[190,191] SECCM is a premier technique for structure–function–activity studies in electromaterials science, with high sensitivity, fast time response, and high spatial resolution.[192] The disk shape of the electrode provides a flat surface which enhances the imaging and mapping resolution for microscopy or modeling. Methods to decrease the tip size allow better spatial resolution and cavity nanopipettes enhance the sensitivity for nanotip SECM imaging.[193] Thus, electrodes with different shapes may increase the spatial resolution and sensitivity for electrochemical imaging.

Conclusions

This review summarizes the fabrication and application of carbon-based electrochemical sensors with various shapes. For decades, extensive studies were focused on carbon material properties, but recent studies demonstrate how the shape of the microelectrode influences the electrochemical performance and enhances specific functions. The nanostructure of carbon electrodes that is introduced by carbon nanomaterials enhances sensitivity and electron transfer kinetics compared to pristine CFMEs. Trapping electrodes with porous films and large surface roughness enable high-selective detection of some neurotransmitters that are hard to differentiate at flat electrodes, such as catecholamines. The enhanced side reactions are observed in the voltammograms that are obtained from trapping electrodes.

To date, almost all ultra-small carbon electrodes are micron-scale, which limits the application of intracellular sensing. Nanosized electrodes are capable of synapse probing

and implantation with minimum tissue damage and reduced ohmic drop. 3D-printed carbon electrodes are precisely built to submicron scaled cone-, sphere- and needle-shape to meet different requirement in biological applications. In the future, tunable and flexible sensor fabrication will be more adaptable for different types of probing tools. Combined with multiplexed analytical techniques, carbon microelectrodes will be applied in multiple fields in electrochemical sensing, such as single-cell measurement, multichannel measurement and *in vivo* studies. Nanopipettes with a cavity have applications beyond electrochemical sensing, such as cell and vesicle counting. Additionally, with the development of microdevices, portable multifunctional carbon-based sensors will have applications in clinical fields.

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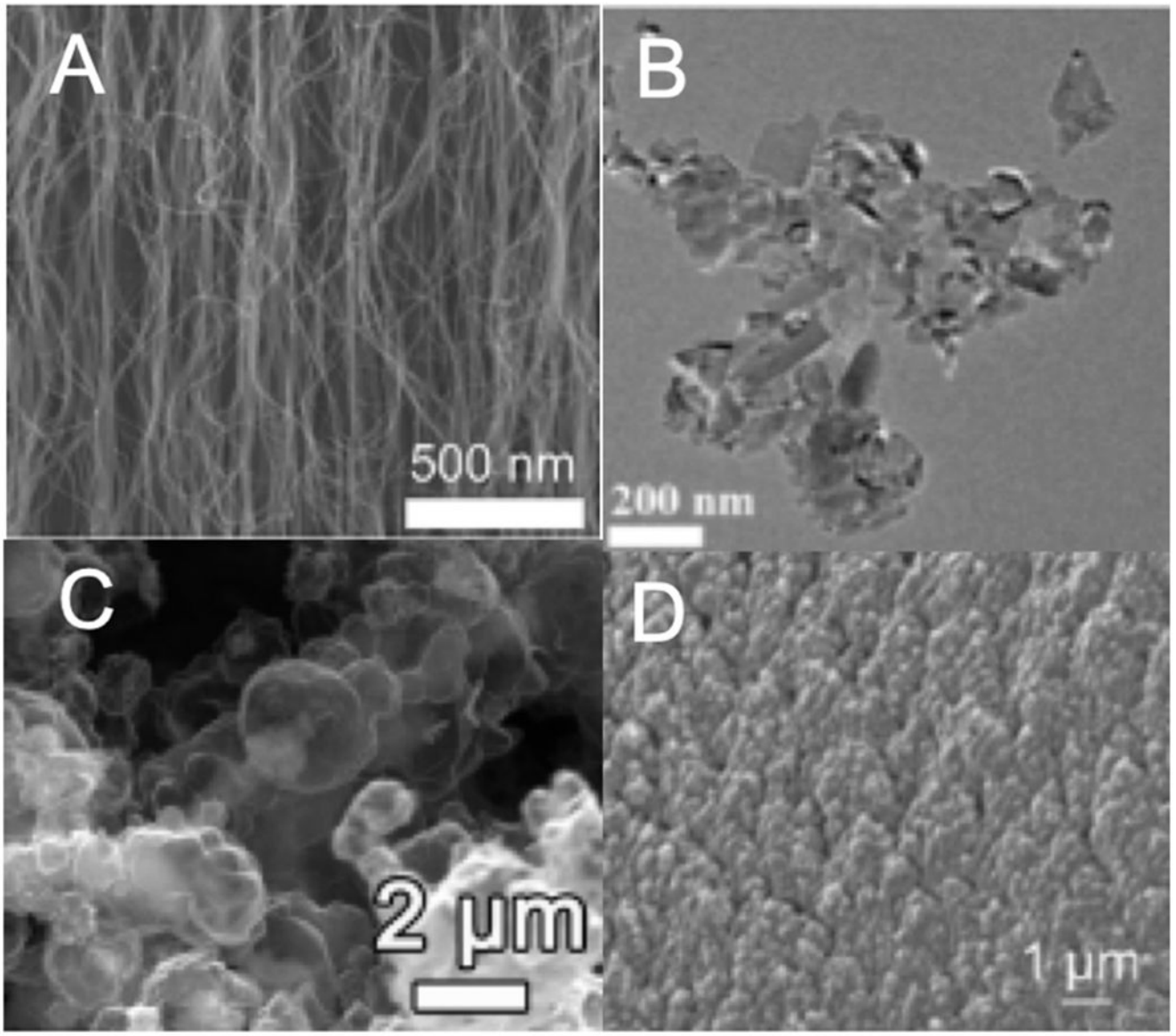

Figure 1.

Different carbon allotropes. (A) scanning electron microscopic (SEM) image of vertically-aligned MWCNT synthesized via CVD catalyzed by a thin film of Fe and aluminum oxide.[63] (B) Transmission electron microscopic (TEM) image of nanodiamonds purchased from FND Biotech, Inc., Taiwan.[16] (C) SEM image of *in situ* synthesized 3D printed graphene foam.[28] (D) SEM image of carbon nanospikes synthesized via PECVD.[13] Panels A, B, C are reprinted by permission from American Chemical Society and Panel D from Elsevier.

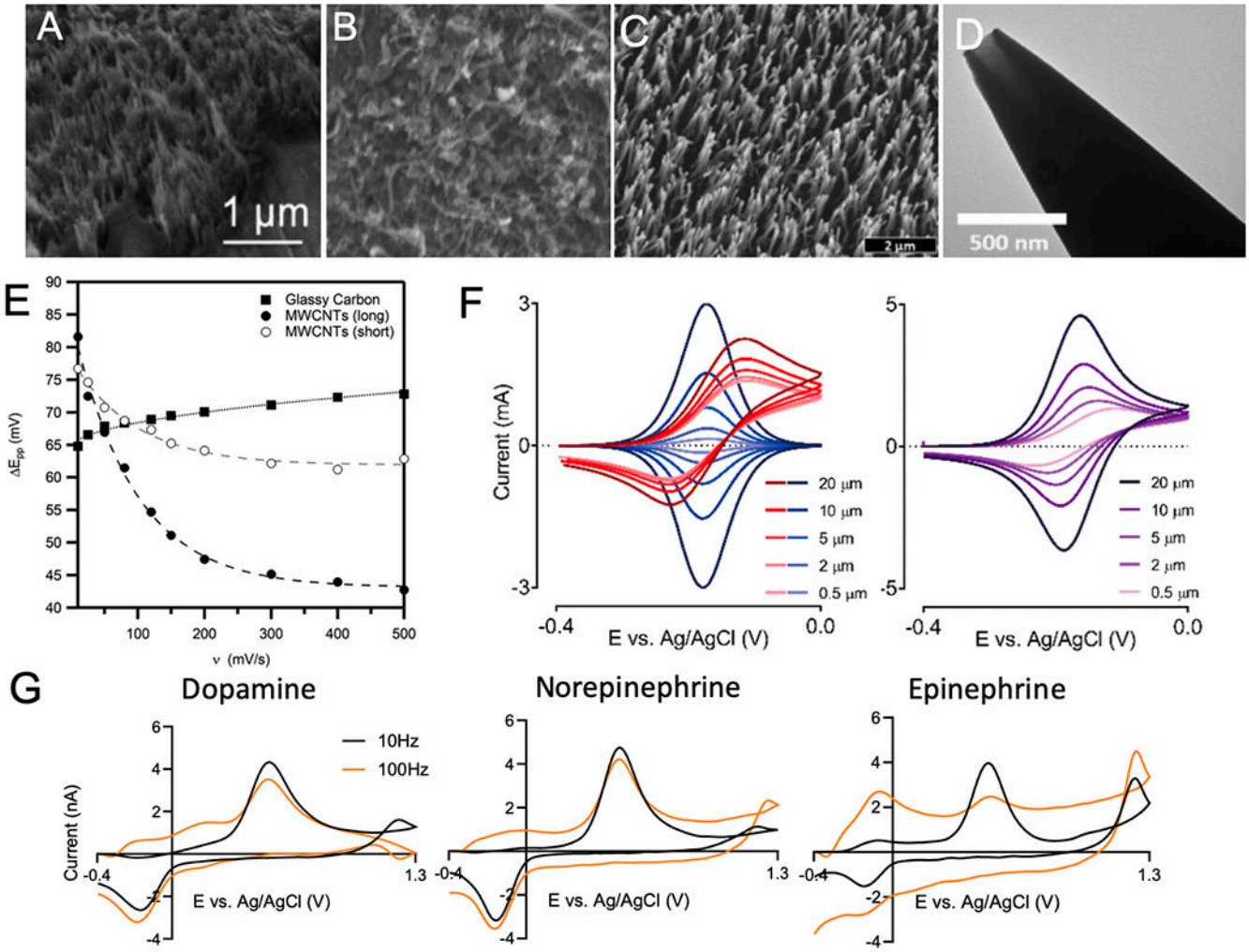

Figure 2.

SEM images of carbon-based microelectrodes that exhibits thin-layer diffusion for mass transport. (A) CNTYMEs trap molecules in the crevices of CNT forests.[10] (B) MWCNT/ta-C composite carbon electrode trap molecules in the porous film on the electrode surface.[80] (C) MWCNT modified glassy carbon exhibit thin-layer diffusion due to the dense and long CNT arrays on the surface.[81] (D) CNPEs with a nano-sized tip trap molecule inside the cavity.[23] (E) ΔEp vs scan rate of glassy carbon, long MWCNTs and short MWCNTs in 1 mM $Ru(NH_3)_6Cl_2$.[81] (F) Simulated cyclic voltammograms of CNT yarn electrodes with varying length (longer length is darker color) in 1 μM $Ru(NH_3)_6Cl_2$. Blue: currents of thin layer model; Red: diffusion model; Purple: total currents.[18] (G) FSCV of dopamine, norepinephrine, and epinephrine at FSCV repetition rates of 10 Hz (black) and 100 Hz (orange) at CNTYMEs.[10] Panels A, C, F and G reprinted by permission from American Chemical Society. Panels B, D, E reprinted by permission from Elsevier.

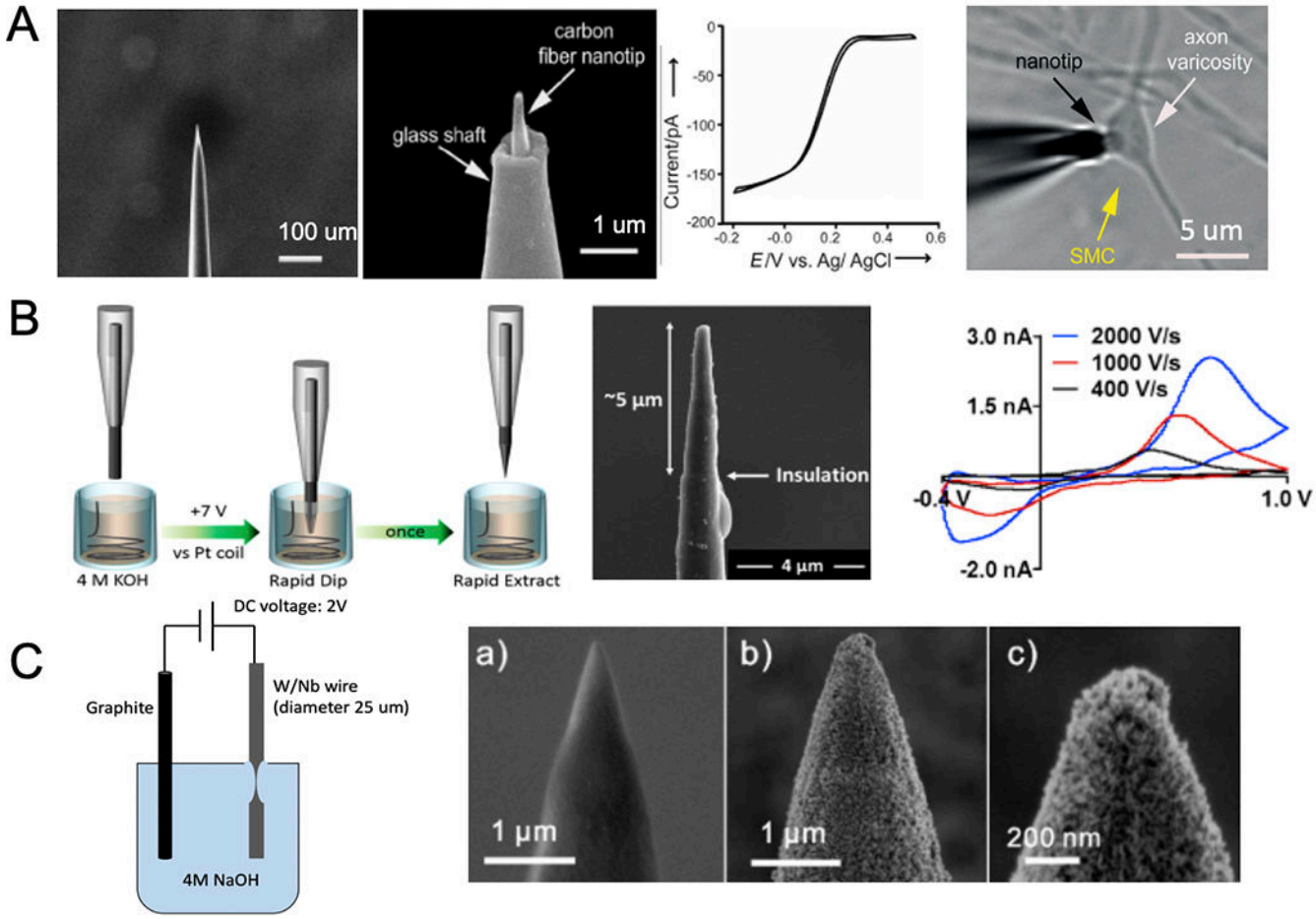

Figure 3.

Different designs of carbon nanoelectrodes. (A) Fabrication of CFNE via flame etching. A piece of flame-etched carbon fiber with conical nanotip was inserted into the glass micro-pipette and well-sealed.[99] The CV of 1 mM potassium ferricyanide at a CFNE. The nanotip was inserted inside a synapse between a varicosity of a superior cervical ganglion neuron and smooth muscle cell. (B) Carbon fiber nanoelectrode (CFNE) fabrication scheme via wet etching. The cylindrical CFME was dipped in 4M KOH solution and applied a potential of +7 V. CFME's was etched to nano-size after rapid dipping and extraction.[101] CVs of 2 µM dopamine collected at varying scan rates. (C) CNS-coated nanoelectrode fabrication. A piece of tungsten or niobium wire (25 um diameter) was wet-etched in the 4M NaOH solution by applying DC voltage of 2 V. The metal wire with nanotip was then coated with CNS.[15] Panel A is reprinted by permission from Wiley, panel B from the American Chemical Society, and panel C from Royal Society of Chemistry.

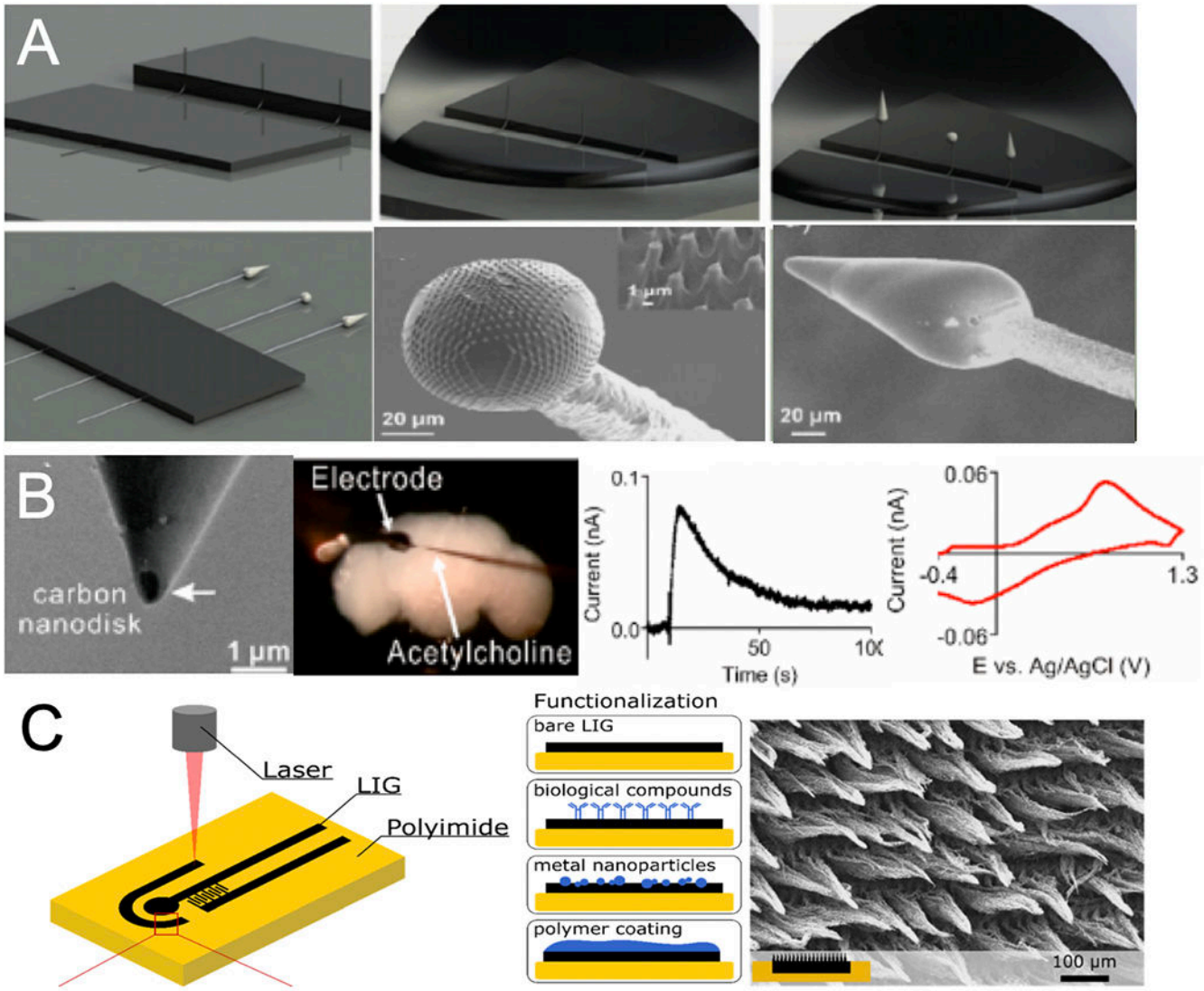

Figure 4.

Designs of complex 3D printed carbon microelectrodes. (A) A process flow of 3D printing electrode fabrications via two-electron lithography and SEM images of two designs, including sphere-shape with nano-sized spikes and cone-shape carbon microelectrodes. With laser assisting, SU-8 photoresist was polymerized at the metal wire tip with desired structure, and then pyrolyzed to carbon.[29] (B) SEM image of the 3D-printed carbon nanoelectrode. The nanoelectrode was then implanted in an adult fruit fly brain to detect stimulated dopamine. [30] (C) The synthesis of laser-induced graphene from polyimide film with designed pattern.[114] Panel A, C are reprinted by permission from American Chemical Society and panel B from Wiley.

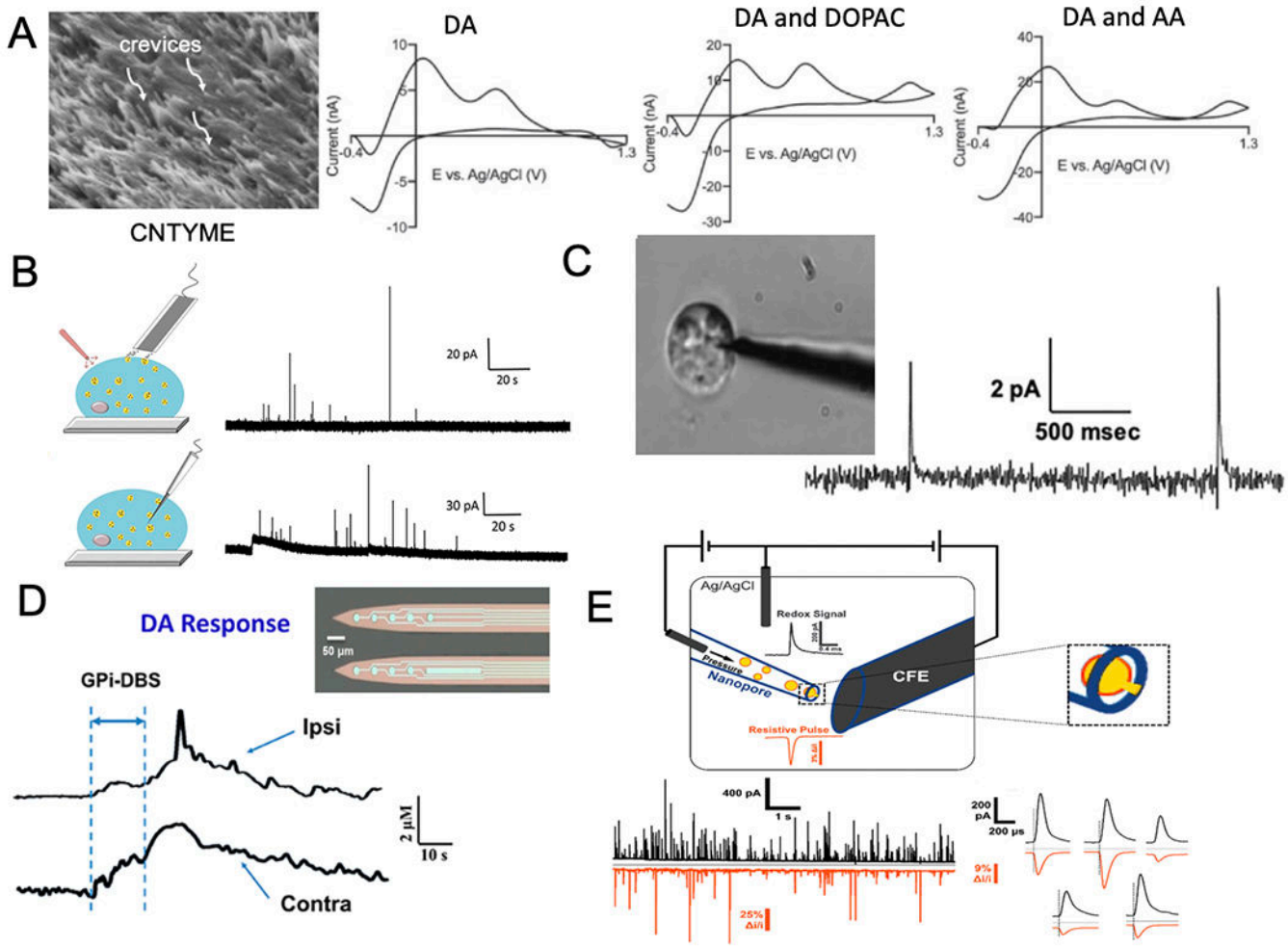

Figure 5.

Applications of customized carbon electrodes. A) Discrimination of dopamine in the presence of DOPAC and ascorbic acid on CNTYMEs. The CVs are obtained at pH 8.5, 100 Hz.[19] B) Exocytosis and vesicular content in BON cells. Single cell amperometry (SCA) combined with a disk-shape microelectrode (top), flame-etched CFME was used for the exocytosis detection via intracellular vesicle impact electrochemical cytometry (IVIEC).[100] C) Etched carbon fiber nanotip for recording of nanoscale vesicles individually encountered in the cell cytoplasm.[101] D) Modified microelectrode arrays for rapid dopamine detection under deep brain stimulaton.[165] E) An integrated nanopore/microelectrode sensor for high-throughput detection of redox-filled liposomes.[166] Panel A is reprinted by permission from The Electrochemical Society, panel B is from Wiley and panel C, D, E are from American Chemical Society.

Table 1.

Carbon nanomaterials that are synthesized by CVD for electrochemical sensing.

Carbon material	Deposition technique	Substrate	Ref
Microcrystalline BDD	MW-PACVD	Si/SiO2	64
Nanodiamond	MW-PACVD	Carbon fiber	65
Graphene	CVD	Polyimide	66
Graphene	CVD	Si/SiO2	67
3D graphene foam	CVD	Ni Powder	49
CNT yarn	catalytic CVD	Si/SiO2	68
MWCNT	Low temperature CVD	Ti	69
MWCNT	Drop-casting	Au	70
Long MWCNT	Water-assisted CVD	Si	57
CNS	PECVD	Ni	13
CNT pillars	CVD	Quartz	32

Abbreviations:

BDD: boron-doped diamond; CNT: carbon nanotube; MWCNT: multi-walled carbon nanotube; CNS: carbon nanospike; MW-PACVD: microwave plasma-assisted chemical vapor deposition; CVD: chemical vapor deposition; PECVD: plasma-enhanced chemical vapor deposition.

Table 2.

The electrochemical performance of carbon microelectrodes in neurochemical detections.

Electrode material	Analytes	Remarks	Methods	Ref
CNT yarn	DA, NE, EP	Selective detection of catecholamines	FSCV	10
CNPE	DA	High spatial resolution	FSCV	23
Nanodiamond/CFME	DA, 5HT, etc.	Antifouling	FSCV	17
CNS	DA	High sensitivity and fast electron transfer kinetics	FSCV, CV, EIS	13
CNT/CF	DA, AA, UA	Simultaneous detection	DPV, CV, EIS	62
MWCNT/GC	DA	Mass transport change due to morphology	CV	81
ND/ta-C	DA	Improved sensitivity	CV	45
Diamond	DA, DOPAC, AA	Selective detection of DA with interference	CV, SWV	130
CNT fiber/yarn	DA, UA, 5HT, etc,	High sensitivity, selectivity and temporal resolution	FSCV	126
3D-printed carbon	DA	High spatial resolution	FSCV	30
LIG	H2O2	High sensitivity	CV, Amperometry	109
ND/GC	Sulfanilamide	High sensitivity and selectivity	CV, SWV	155
Microneedle	Glucose, UA, cholesterol	Multi-channel	Amperometry	35
SWCNT/GC	DOPAC	High sensitivity	CV	156
3D fuzzy graphene	DA	High spatial resolution	FSCV	157
Carbon paste	H2O2	Metal organic frame work and high selectivity	CV	158
Carbon paste	ATP	Sensitive electrochemical determination	CV	159
Carbon paste	Adenosine	Electrochemical determination in serum	CV, SWV	160
Graphene/GC	Adenosine, theophylline	Real-time detection in urine and blood samples	CV, DPV	161
MWCNT/GC	Histamine	High sensitivity	CV, DPV	162
SPE/SWCNT	Histamine	Flexible electrochemical sensor	CV	163
SPE/MWCNT	5HT	Low limit of detection	CV, SWV	164

Abbreviations:

CNPE: cavity-nanopipette electrode; CF: carbon fiber; SWCNT: single-walled carbon nanotube; GC: glassy carbon; ND: nanodiamond; ta-C: tetrahedral amorphous carbon; SPE: screen-printed electrode.

DA: dopamine; NE: norepinephrine; EP: epinephrine; 5HT: serotonin; AA: ascorbic acid; UA: uric acid; DOPAC: 3,4-Dihydroxyphenylacetic acid. FSCV: fast-scan cyclic voltammetry; CV: cyclic voltammetry; EIS: electrochemical impedance spectroscopy; DPV: differential pulse voltammetry; SWV: square wave voltammetry.