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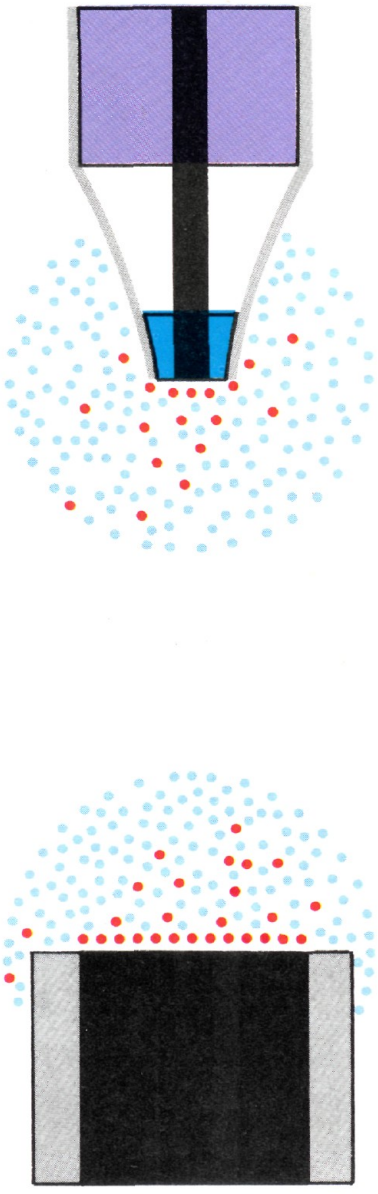
Microvoltammetric Electrodes



In every area of analytical chemistry it seems that smaller is better. For example, capillary columns for gas and liquid chromatography are rapidly replacing the conventional columns because they lead to increased resolution. Mini-inductively coupled plasma torches have been developed that result in considerable savings in operating expense. Microcomputers, with their increased capabilities, are rapidly becoming the method of choice for laboratory automation. As will be shown, small also has many advantages in voltammetry. Disk-shaped voltammetric electrodes of less than 10-μm radius have recently been fabricated. These electrodes are approximately 10 times smaller in diameter than a human hair, and because of their very small size they exhibit very different voltammetric properties than do electrodes of conventional size. In this REPORT, these very small chemical sensors will be referred to as microvoltammetric electrodes.

One may well ask, why in the world would you want to make such a small electrode? An obvious answer is that if you have a very small place in which you wish to make a chemical measurement, you have a need for such a device. Our particular interest in microvoltammetric electrodes arose because of our desire to make measurements of chemical concentrations inside the mammalian brain. The specific compounds that we, as well as a number of other groups, are interested in measuring are a class of small molecules referred to as neurotransmitters.

Neurotransmitters have a very important role in the brain since they are the key link in communication between neurons. Four of the known neurotransmitters, dopamine, norepinephrine, epinephrine, and serotonin, are easily oxidized at carbon electrodes and, thus, in vivo voltammetry provides a unique way to monitor chemical changes arising from neuronal actions. These four neurotransmitters are of special interest to researchers in neuroscience since several different types of drugs, such as amphetamine, cocaine, and various neuroleptics, are known to have their sites of action in the brain, where these neurotransmitters operate. They have also been implicated in various disease states. A review that describes the function of neurotransmitters in greater depth has appeared in this JOURNAL (*1*). As will be shown later in this REPORT, very interesting information concerning drug-induced changes in concentration of chemical compounds in the mammalian brain can be obtained by using microvoltammetric electrodes.

Besides the unique size of microvoltammetric electrodes, there are several other features that make them useful in various forms of chemical analysis. We have investigated many of these since it is absolutely necessary that an analytical tool be well understood before it is used in a unique en-

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vironment such as the mammalian brain. One notable feature of microvoltammetric electrodes is that they enable time-independent currents to be easily monitored. This feature simplifies measurements and facilitates their use under conditions where variations in potential are disadvantageous. The currents at these electrodes are extremely small, and the electrodes are, therefore, virtually nondestructive of the species being electrolyzed. Furthermore, because of the small currents, the electrodes can be used in solutions of very high resistance. The equations describing these features of microvoltammetric electrodes have been recognized for a number of years. Thus, one of the advantages of working in this field is that detailed derivations for the expected current–voltage response are given in the literature, and these can be directly applied to chemical systems. However, only recently have microvoltammetric electrodes been constructed.

Current–Voltage Curves

Effects of Diffusion. The goal of most voltammetric experiments, including in vivo electrochemistry, is to generate a current–voltage curve from which the chemist can extract a half-wave potential, which can be used to identify the species in solution; the amplitude of the current can be related directly to the concentration of the species in solution. Unfortunately, these parameters are not easy to obtain in a straightforward fashion in most electrochemical experiments done in stationary solutions.

Let's first consider cyclic voltammetry at a microvoltammetric electrode done at a relatively fast scan rate (10 V/s). In cyclic voltammetry, the voltage is scanned in a triangular fashion, and the resulting current measured. Most cyclic voltammograms have a peak-shaped current–voltage curve as shown for the oxidation of ferrocene in acetonitrile in Figure 1a. The initial potential, 0.0 V in this example, is selected as a place where no electrochemistry is occurring. As the potential is scanned in a positive direction, the half-wave potential for ferrocene is approached and the current starts to increase. However, as electrolysis of the compound decreases its concentration at the electrode surface, the current returns toward the baseline after reaching a maximum. This occurs because the electrolysis rate greatly exceeds the rate at which the species can diffuse to the electrode surface. At these rapid time scales, the majority of the diffusion is perpendicular to the electrode surface (Figure 2) (2). Therefore, both diffusion and concentration information are convoluted in the current–voltage curve. On the reverse

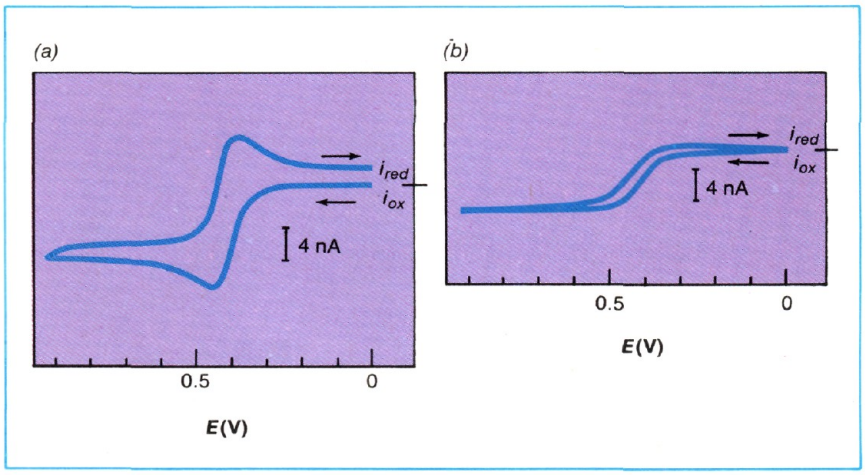

Figure 1. Cyclic voltammogram of ferrocene (1.0 mM) in acetonitrile with 0.1 M tetra-*n*-butylammonium perchlorate at a gold microdisk electrode (r = 6.5 μm). (a) 10 V s^{-1} scan rate. (b) 0.1 V s^{-1} scan rate

half of the triangular voltage sweep, the electrolysis products (ferricinium ions in this example) can be reduced, resulting in current flowing in the opposite direction. Although the data given in Figure 1a were obtained at a microvoltammetric electrode, this type of response is also obtained at an electrode of conventional size (radius ≃1 mm).

If we do the experiment again, but at a slower sweep rate, the results given in Figure 1b are obtained. Again, the potential was scanned from 0.0 V toward positive potentials. The increase in current in the vicinity of the half-wave potential is still well-defined but, under these conditions, the current at more positive potentials is essentially steady-state and, thus, is easier to use for measuring concentration. The steady-state current arises because the electrolysis rate is approximately equal to the rate of diffusion of molecules to the electrode surface. At the slower scan rate, radial diffusion to the edges of the surface of the disk-shaped electrode as well as diffusion perpendicular to the surface becomes important (Figure 2). When the direction of the potential sweep is reversed, the current essentially follows that obtained with the initial scan because the products of electrolysis have diffused away from the electrode. At an electrode of larger size, this type of effect is difficult to observe because the scan rate must be very slow for the radial diffusion to contribute appreciably to the current (see below).

In both voltammograms shown in Figure 1, diffusion plays an important role in the shape of the current–voltage curve. Theoretically, one can carry this argument even further. If an electrode of 10-nm diameter could be constructed and used at the same sweep rates as shown in Figure 1, the resulting current would be an exponential function of potential. At these very small electrodes, the rate of elec-

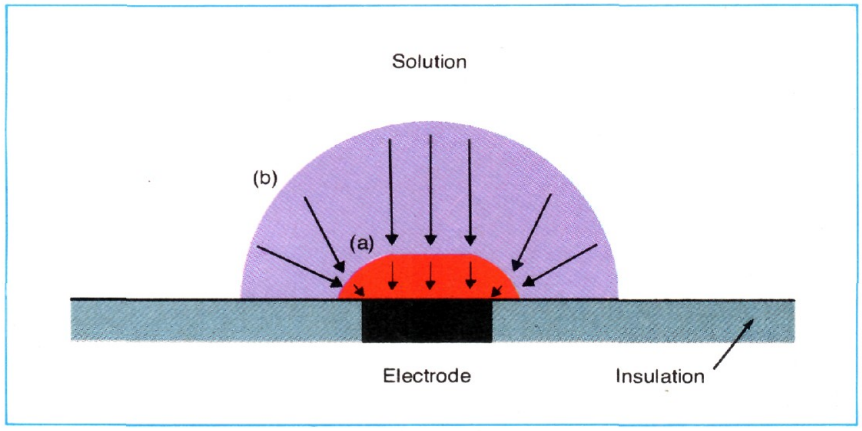

Figure 2. Diffusion profile of electrolyzed species at a microvoltammetric electrode. (a) Profile at short times as in rapid cyclic voltammetry (10 V s^{-1}). (b) Profile at longer times as with slower scan rate cyclic voltammetry (0.1 V s^{-1})

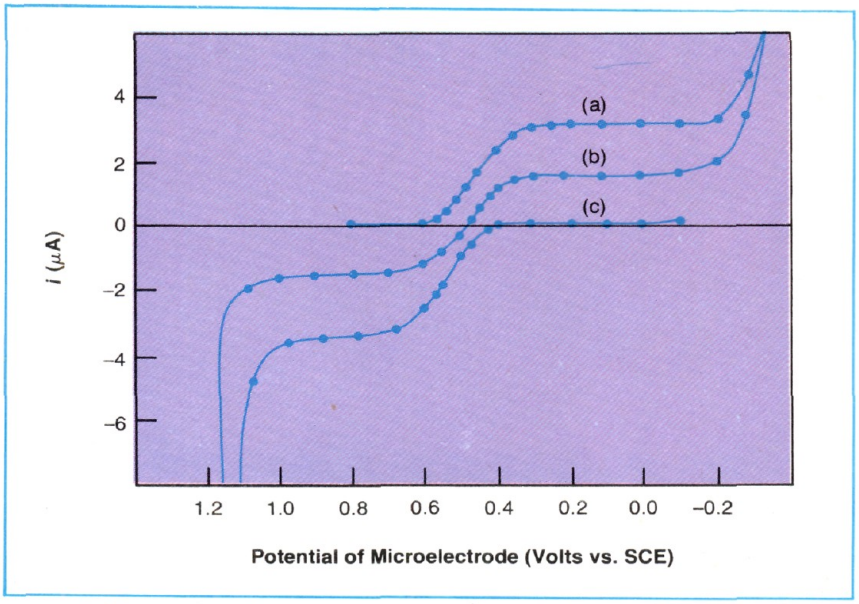

Figure 3. Electrolysis of ferrous chloride and ferric chloride in 0.5 N hydrochloric acid. Curve a, 0.002 M $FeCl_3$; curve b, 0.001 M $FeCl_2$, 0.001 M $FeCl_3$; curve c, 0.002 M $FeCl_2$. Reprinted by permission

trolysis of molecules would be so reduced relative to the rate of diffusion of molecules to the electrode that electrolysis would become the rate-determining step, and the current–voltage curve for a reversible system would be given by the Nernst equation.

The steady-state contributions to the current have been colloquially referred to as edge effects (or, at spherical electrodes, as spherical effects) and have been recognized by electrochemists for a number of years. In fact, in 1941, Laitinen and Kolthoff introduced the term *voltammetry* to describe steady-state current–voltage curves (*3*). Working with disk electrodes of the size commonly used in the electrochemical laboratory today (diameter ≃3 mm), they obtained the curves shown in Figure 3. Each point on these curves was measured at a fixed, applied potential that was monitored for "two or three minutes" so that the time-dependent effects of diffusion would be minimized. The current was then recorded and the voltage changed to the next desired value. This procedure was necessary at this larger-size electrode because the ratio of the number of molecules diffusing perpendicular to the electrode relative to those diffusing in at the edges is much greater at an electrode of this size, and the steady-state response is not observed for a much longer time. This approach to voltammetry often gives irreproducible results because natural convection also affects transport of molecules to the surface at these time scales.

As shown above, the measurement of sigmoidally shaped voltammograms at electrodes in stationary solutions is not new—it is simply easier to do with the newly developed microvoltammetric electrodes. These microvoltammetric electrodes do not have to be disk-shaped. Cylinders, spheres, rods, and virtually any other geometry of electrode of small enough size will also give the same result.

The time scale of the measurement and the radius of the electrode affect the type of voltammogram that one obtains in stationary solutions. At fast time scales, or at electrodes of large radius, peak-shaped voltammograms are obtained, whereas with small radius or with long time scales of measurement, steady-state voltammograms are obtained. Electrodes of intermediate size (or measurements at intermediate scan rates), of course, give intermediate results: Time-dependent and time-independent currents are superimposed.

Effects of Chemical Rate Constants. The rates of chemical reactions occurring in solution and the rate of electron transfer with the electrode can also affect the shape of the current–voltage curve. If the rate of electron transfer of the species in solution with the electrode is slow, this can distort the current–voltage curve, giving a drawn-out response. Fleischmann's research group at Southampton has extensively studied the rate of electron transfer at small electrodes and finds it to be comparable to that of electrodes of conventional size (*4*). However, because the effect of diffusion on the electrochemical signal is less pronounced, faster heterogeneous rate constants can be measured at microvoltammetric electrodes. Although this is interesting from a fundamental electrochemical point of view, to the practicing electroanalytical chemist it simply means that the rate of electron transfer may distort the current–voltage curve even more at microvoltammetric electrodes than at electrodes of larger size. To get rid of this distortion, the electrochemist can do little except change electrode materials, change the solution conditions, pick another compound to analyze by electrochemical techniques, or, perhaps, chemically modify the surface of the electrode.

An effect of equal concern to analytical use of electrochemistry is the presence of chemical reactions that precede or follow the initial electron transfer and that also contribute to the current, since these may also distort the predicted current–voltage curve. The theoretical effect of this type of reaction has been extensively studied and several of the derivations of the current response have been compiled by Galus (*5*). Fortunately for chemists working with microvoltammetric electrodes, these derivations have been considered for electrodes of all sizes. These derivations show that chemical processes that follow the initial electron transfer and are of moderate rate will have much less of an effect on the current at microvoltammetric electrodes than at larger electrodes. To see why this is true, let's examine a reaction of the type

$$O \xrightarrow{ne} R \xrightarrow{k_c} O + Y$$

This reaction is referred to as a catalytic reaction because the initially reduced species, O, is regenerated by a chemical reaction with a pseudo-first-order rate constant, k'_c. At a large electrode, this regenerated O will return to the electrode surface, resulting in an increased current. However, at a microvoltammetric electrode with moderate values for k'_c, very little enhanced current is obtained. This result is easily rationalized when one realizes that the average distance into solution that R diffuses before reacting to form O, given by $(Dt)^{1/2}$, where t is the half-life of the reaction and D is the diffusion coefficient, is larger than the radius of a microvoltammetric electrode. Thus, while the distance that R diffuses is not far, at a microvoltammetric electrode a large part of the regenerated oxidant is removed from the vicinity of the electrode surface and, thus, a minimal catalytic contribution to the current is observed. The decreased effect that a catalytic reaction has at microelectrodes has been demonstrated for the oxidation of dopamine in the presence

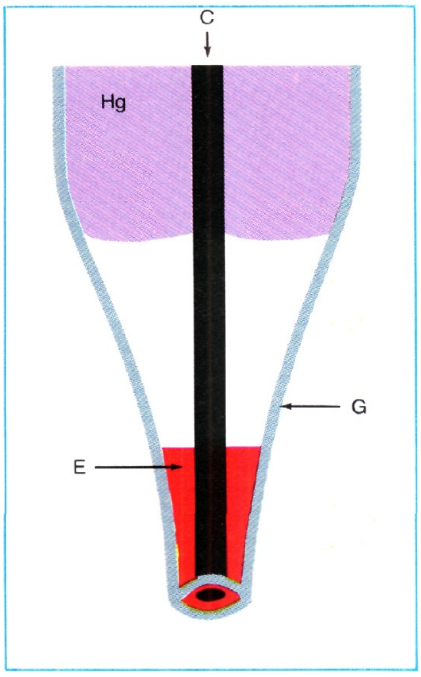

Figure 4. Glass capillary, disk-shaped microvoltammetric electrode. C, carbon fiber; G, glass; E, epoxy to prevent leakage; Hg, mercury for electrical connection

of ascorbic acid, conditions at which catalytic reaction is known to occur (*6*). This reaction is of importance in the measurement of dopamine in the brain since ascorbic acid is present in large concentrations in extracellular fluid and thus could distort measurement of extracellular dopamine.

The same qualitative arguments can be made for other types of chemical reactions following the electron transfer. This is important in chemical analysis, since determinations are often made in solutions of unknown composition (especially in vivo) where these types of reactions are likely to occur.

Electrodes and Instrumentation

We have employed carbon fibers, obtained from various commercial sources such as Hercules, Inc., Union Carbide Corporation, and Courtauld, Ltd., in the construction of microelectrodes. These fibers have diameters in the range of 6–12 μm (*6*, *7*). They are formed from the high temperature pyrolysis of materials such as polyacrylonitrile or pitch and are intended for use in golf clubs, bicycle frames, etc. Our method of construction is relatively simple and results in the fiber being sealed with epoxy in a glass capillary (Figure 4). Approximately 50% of the electrodes constructed are useful for electroanalysis. Double-barreled pipets can also be constructed, with the second barrel used as the reference electrode or as a second carbon fiber electrode (*6*).

Several other types of microvoltammetric electrodes have been described in the literature. Ponchon et al. were the first to use carbon fibers for microvoltammetric electrodes (*8*). Their electrodes have approximately 500 μm of the fiber protruding from the glass capillary, resulting in a cylindrical electrode. This design results in a larger faradaic current, but the voltammograms exhibit non-steady-state behavior at 300 mV s^{-1}. Swan has described micro-disk electrodes fabricated from platinum and tungsten wires (*4*). These wires were electrochemically etched to form electrodes with diameters as small as 1 μm as determined by the limiting diffusion currents. McCreery has constructed cylindrical microvoltammetric electrodes from carbon fibers and 7-μm-radius gold wires for use in spectroelectrochemical applications (*9*).

Microvoltammetric electrodes connected in parallel maintain the features of single microvoltammetric electrodes with the advantage of increased current amplitudes. These have been fabricated using thin film technology (*10*) or photoetching techniques (*11*). As expected, the steady-state current is maintained, but the current is increased by the sum of the small electrodes.

An obvious limitation in the use of single microvoltammetric electrodes is that very small currents must be measured. For electrochemical measurements in the millisecond time range, where very little electronic filtering can be employed, we make all of our measurements in a faraday cage. The EG&G Princeton Applied Research Corporation Model 174A is useful for measurements down to 10 pA. For measurements of dilute concentrations at slow scan rates, commercial picoammeters can be used. We recently built a current transducer capable of low noise subpicoamp measurements, which is ideal when rapid potential pulses (92 ms) are employed. Using this repetitive pulse waveform, we can measure concentration changes of 1×10^{-7} M for the $2e^-$ oxidation of dopamine in pH 7.4 buffer. In these measurements, the current is integrated over 34 ms, during which time only about 60 000 molecules are oxidized! Obviously, measurements of much lower concentration at microvoltammetric electrodes are going to require a new approach to potentiostat design.

Other Features of Microvoltammetric Electrodes

The concentration is perturbed by electrolysis only a very small distance from the microvoltammetric electrode (approximately six times the radius under totally steady-state conditions) (*12*). Therefore, microelectrodes are not greatly affected by movement in solution. In fact, the steady-state current density observed at microvoltammetric electrodes of 4-μm radius is equivalent to that observed at a rotating disk electrode operated at 500 rps, a relatively fast rotation speed. This feature is of particular importance in applications of "polarographic" oxygen electrodes in biological systems, where variable convective rates may occur.

Microvoltammetric electrodes show great potential utility for very fast measurements since double-layer charging currents should be proportional to the electrode area. This prediction of decreased charging current times is important since this parameter determines the shortest time at which meaningful measures of faradaic current can be made. For a potential pulse, the charging current (i_{DL}) is

$$i_{DL} = \frac{\Delta E}{R} e^{-t/RC} \qquad (1)$$

where ΔE is the amplitude of the pulse, R is the resistance of the electrochemical cell, C is the double layer capacitance, and t is the time measured from application of the pulse. The double-layer capacitance decreases exponentially with a decrease of the area, while the time-dependent faradaic current decreases linearly with area. Thus, the faradaic/charging current ratio should be increased at a microvoltammetric electrode. For a disk electrode of 4-μm radius, the double layer should be 99% charged within 3 μs, even assuming a 100 μF cm^{-2} double-layer capacitance and a cell resistance of 10 kΩ. With this response, very rapid time-dependent measurements of chemical events could be made. Unfortunately, we have not been able to experimentally verify this prediction. Nonfaradaic currents at carbon fiber electrodes are observed that restrict faradaic measurements to the millisecond time domain. Possible sources of this residual current are microcracks in the carbon formed during the process of fabrication, or surface oxides on carbon. A clever approach to these problems has been taken by McCreery, who ignores the current and uses spectroelectrochemistry to monitor electrolysis on carbon fiber electrodes (*9*). Using a laser with a highly aligned optical system, he has observed electrochemically generated products along the axis of a carbon fiber within 5 μs of a potential pulse.

An area in which microvoltammetric electrodes should be of great importance is in the study of redox systems in highly resistive solvents. Electrochemical currents at disk electrodes of 4-μm radius are 4 to 5 orders

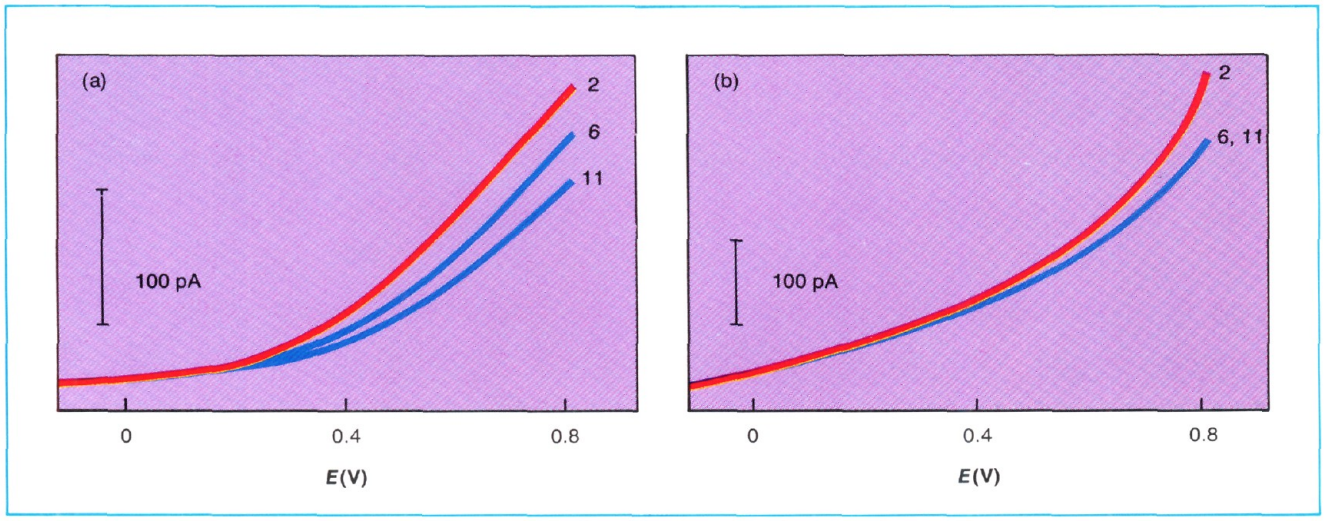

Figure 5. Voltammograms from an electrode implanted in the caudate nucleus of an anesthetized rat. Numbers refer to scan after implantation. 20 mV s^{-1} scan rate. (a) Linear sweep voltammetry. (b) Back-step corrected normal pulse voltammetry

of magnitude smaller than those seen at electrodes of conventional size. Since less current is passed, iR problems are much less severe, as previously noted. We have recently examined the oxidation of ferrocene in acetonitrile with low concentrations of tetra-*n*-butylammonium perchlorate as supporting electrolyte. Nernstian behavior is observed with a disk electrode of 6.5-μm radius even with supporting electrolyte and depolarizer both at 10^{-3} M. With the same conditions, the cyclic voltammogram at a Pt electrode of 400-μm radius has 240 mV peak separation! (Ideal behavior is 59 mV peak separation for $n = 1$.) These results demonstrate that electrochemistry without correction for iR effects is now feasible in solutions of very high resistance.

Applications

As previously discussed, microvoltammetric electrodes have an advantage over conventionally sized electrodes in such applications as voltammetry in resistive solutions and the determination of oxygen under conditions of varying convective mass transport. Interest in the area of microvoltammetric electrodes originally arose for the accurate measurement of diffusion coefficients. Although measuring diffusion coefficients is not a particularly stimulating research endeavor, it is of fundamental importance since the knowledge of the values of diffusion coefficients is necessary to interpret electrochemical results. In these types of experiments, a pulsed waveform is generally employed so that the current is measured at a single fixed potential, usually selected so that the surface concentration of the species being oxidized will be zero. Under these conditions at a spherical electrode, the current is given by

$$i = 4\pi rnFCD\left[r\left(\frac{1}{D\pi t}\right)^{1/2} + 1\right] \quad (2)$$

where n is the number of electrons involved in the electrode reaction, F is the faraday, D is the diffusion coefficient, C is the concentration, and r is the radius of the electrode. Inspection of Equation 2 shows that, at sufficiently long times, the current is independent of time. It is also apparent that the time when the steady-state current becomes significant is dependent on the radius of the electrode. Expressions have been derived for electrodes of other geometries, including a disk (*9*), a hemisphere (*6*), and a cylinder (*2*).

As stated at the beginning of this review, our primary interest in microvoltammetric electrodes is to use them as sensors of changes in chemical concentrations of neurotransmitters in the mammalian brain. Obviously, small electrodes are necessary for these in vivo measurements so that the electrode does not destroy the brain region in which measurements are being made. Nerve terminals have diameters in the 1-μm range, so even the electrode shown in Figure 4 is large with respect to these cells. Nevertheless, these electrodes appear to be essentially nonperturbational in brain tissue since the measured current does not change significantly with repetitive potential pulses—a criterion of tissue damage that has been established on theoretical considerations (*13*). Another parameter that is essential for meaningful in vivo measurements is that the electrode response remain constant for long periods of time. The electrode must be implanted in the brain and monitored for at least 8 h in most experiments, so opportunities are not available for electrode resurfacing. Our experience has shown that pulsed waveforms, similar to those used in normal pulse voltammetry, are best for maintaining electrode stability in the extremely complex environment of the mammalian brain. We have designed an instrument that is tailor-made for pulse voltammetry at microvoltammetric electrodes and even provides a method of residual current correction (*14*). Normal pulse voltammograms are steady-state when 92-ms pulses are used. Examples of voltammograms in a region of the brain (the caudate nucleus) containing dopamine, using a linear sweep and a pulsed waveform, are given in Figure 5. As shown in the upper half of Figure 5, the current response decreases with successive linear potential sweeps, indicating the instability of the electrode. However, as shown in the lower part of Figure 5, enhanced stability is observed using the pulse technique.

The potential range of the scans given in Figure 5 includes the half-wave potential for the oxidation of dopamine. Voltammograms of dopamine are sigmoidal, but dihydroxyphenylacetate, a major dopamine metabolite, and ascorbic acid both give drawn-out voltammograms as a result of their slow rate of charge transfer with carbon fiber electrodes (*6*). Thus, although these three compounds have a very similar formal potential and are all present in this brain region, the carbon fiber electrodes that we use are most sensitive to dopamine at 0.3 V because of the difference in charge transfer rates. As mentioned previously, interference via the dopamine–ascorbate catalytic reaction is also minimized at these electrodes. Since in

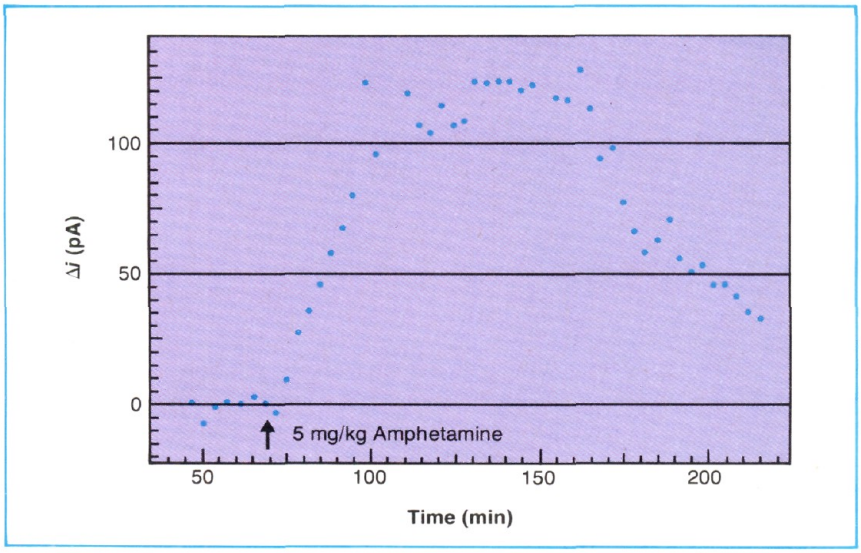

Figure 6. Change in current (Δi) at a microelectrode implanted in the caudate nucleus of an anesthetized rat for repetitive potential steps to 0.35 V vs. SCE following intraperitoneal amphetamine administration

vivo electrochemistry is a relatively new technique, this partial selectivity is important because it is unclear whether dopamine, dihydroxyphenylacetate, ascorbic acid, or some other electroactive compounds change in concentration with neuronal stimulation (*15*, *16*). The in vivo voltammograms from anesthetized, unstimulated rats (Figure 5) appear very similar to those obtained for ascorbate in a conventional electrochemical cell and show no evidence for the presence of extracellular dopamine.

To determine whether the electrode would sense changes in chemical composition in this brain region, we administered the drug amphetamine to anesthetized rats. This drug is known to cause the displacement of dopamine from nerve terminals when it is injected into the intraperitoneal cavity of the rat. As shown in Figure 6, the current at our electrode near the dopamine nerve terminal certainly does increase following administration of amphetamine. Since amphetamine itself is not electroactive, the increase in this signal is definitely due to a change in the chemical composition of endogenous species in the extracellular fluid of rat brain. However, careful analysis of the voltammograms obtained after amphetamine injection does not indicate any substantial signal arising from dopamine. These results suggest that some substance other than dopamine increases in concentration to such a significant extent that the signal from any dopamine that is released is simply masked. The identity of the compound or compounds giving rise to this signal is currently unknown. In contrast to the results shown here, Gonon et al., using a chemically modified electrode, found that the electrochemical signal from the same brain region decreases following amphetamine administration (*15*). Since their electrode had different sensitivities to the compounds suspected to be in brain tissue, these results imply that at least two compounds alter in concentration with amphetamine administration. Thus, while the interpretation of in vivo electrochemical experiments is currently undergoing a revision, it is important to note that the electrochemical signals do correlate with behavioral and electrophysiological measures. This suggests that chemical manifestations of neuronal activity can be measured by this method.

Many applications of microvoltammetric electrodes other than in vivo electrochemistry are just starting to appear. Very recently, Cushman and Anderson showed that carbon fiber electrodes are useful in anodic stripping applications (*17*). Schroeder has digitally simulated the results of the stripping experiment at micromercury drops and has found that very high concentrations of metal ions are obtained in the drop simply during the time for the cathodic scan (*18*). This means that the waiting time for metal deposition in the mercury can be greatly minimized. In addition to the "accelerated" mass transport at microvoltammetric electrodes, features such as low current and rapid time response should lead to increased use of microvoltammetric electrodes in a variety of applications. Since a tremendous amount of literature concerning the theoretical limits and capabilities of microvoltammetric electrodes already exists, this new tool for electroanalytical chemists should rapidly expand in use.

Acknowledgment

The clever insights and enthusiastic research of my students have been the major source of our progress in this new area.

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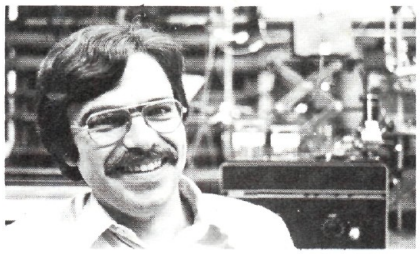

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