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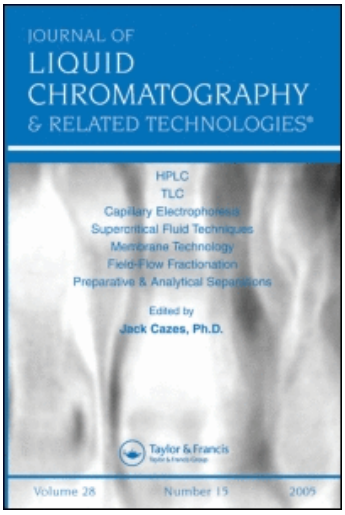

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INTERPRETATIONS OF VOLTAMMETRY IN THE STRIATUM BASED ON CHROMATOGRAPHY OF STRIATAL DIALYSATE

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ABSTRACT

A comparison is made of chronoamperometric data recorded from the striatum and chromatographic data obtained from extracellular striatal perfusate. Three specific cases are considered: the initial sampling period in which a decline in the observed oxidation current occurs; the effect of haloperidol, a dopamine receptor blocker; and the effect of amphetamine. The perfusate is analyzed for ascorbic acid (AA), the dopamine metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). Using the relative response of these compounds at a carbon epoxy or carbon paste electrode, and the relative concentration of each in the extracellular fluid, the expected changes in oxidation currents for the three cases mentioned above are calculated. It is shown that the decline in oxidation current during the initial sampling period is due primarily to a decrease in ascorbic acid. It is also shown that different electroactive components of the extracellular fluid are the cause of changing oxidation currents under different stimulus conditions.

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INTRODUCTION

Work in our laboratory is directed towards development and application of methods for in vivo chemical analysis of the central nervous system. One promising approach for monitoring extracellular neurochemistry in freely moving animals is voltammetry(1-8). There has been some confusion, however, concerning which compounds in the extracellular fluid contribute to the observed oxidation currents at small electrodes implanted in the brain(9). Adams and Marsden have recently reviewed in vivo electrochemical methods and have discussed the problems of interpretation of in vivo voltammetric data extensively(10). For voltammetric recording in the striatum the major concerns are the degree to which ascorbic acid(AA) contributes to the observed increases in oxidation currents following various stimuli and to what extent dopamine and its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) contribute to the increases. The extent that serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) contribute to the oxidation current in the striatum has also been unclear. In addition, it is not clear whether it is always the same neurochemicals causing the increased currents or whether different stimuli (such as amphetamine, neuroleptics, electrical stimulation of the nigrostriatal pathway, feeding, etc.) cause different neurochemical changes which are indistinguishable in the voltammetric measurements. In order to resolve some of these

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questions we began a series of experiments in which the extracellular fluid of the brain is sampled by dialyzed perfusion and analyzed by high performance liquid chromatography with electrochemical detection. The chromatographic results are discussed relative to voltammetric data obtained under similar conditions.

METHODS

Monitoring System

The on-line monitoring system for chromatographic analysis of dialyzed perfusate consists of the components illustrated in Figure 1. The system has two main parts: the perfusion components and the chromatographic components. These two parts connect at the HPLC injection valve. The perfusion components include a model 975 Harvard infusion pump which has been modified to perform simultaneous push-pull perfusion, a three channel fluid swivel(Alice King Chatham Medical Arts, Los Angeles, CA.) located at the top of the test chamber, and a dialysis cannula for perfusion of local brain regions. Two 2.5 ml Hamilton gas tight syringes are used in the infusion pump. These are fitted with three way valves for filling with solution and for removing air bubbles. Artificial cerebrospinal fluid (CSF) flows from the push syringe through the fluid swivel into the dialysis cannula. Low molecular weight components of the extracellular fluid from the surrounding region cross the dialysis membrane

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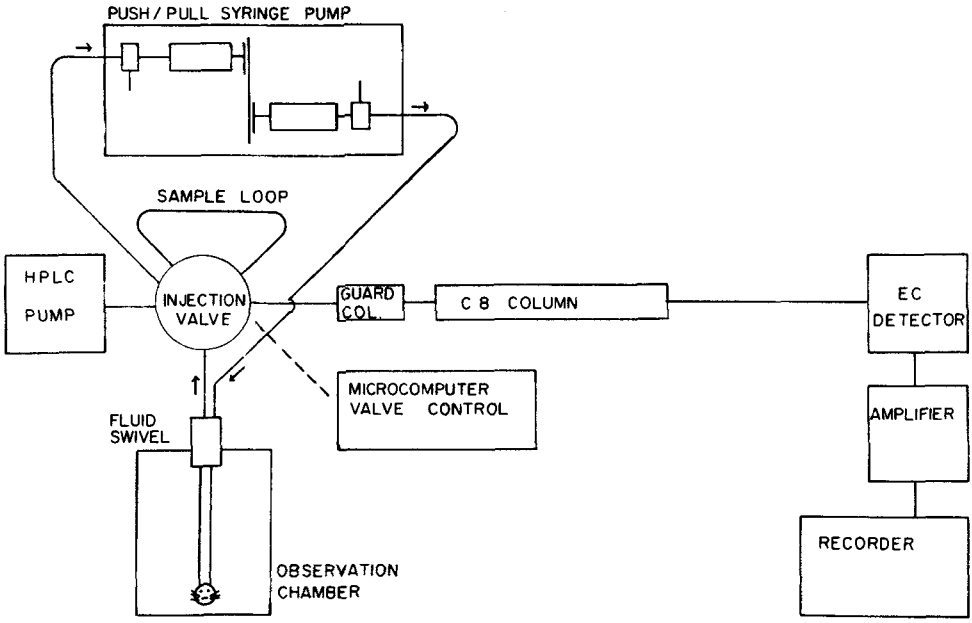

FIGURE 1. Monitoring system for chromatographic analysis of dialyzed perfusate. The pull side of the flow passes through the sample loop of the HPLC system.

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and are carried to the sample loop as the flow leaves the cannula and passes through the fluid swivel to the injection valve (Rheodyne 7010). Model studies characterizing the performance of the dialysis cannula have been described previously(11).

Dialysis Cannula Construction

The dialysis cannula (Figure 2) is constructed from Spectrapor HF hollow fiber dialysis tubing with a molecular weight cutoff of 5000 amu and a diameter of 200 um. To construct the device, the dialysis tubing is cut into 24 mm lengths and

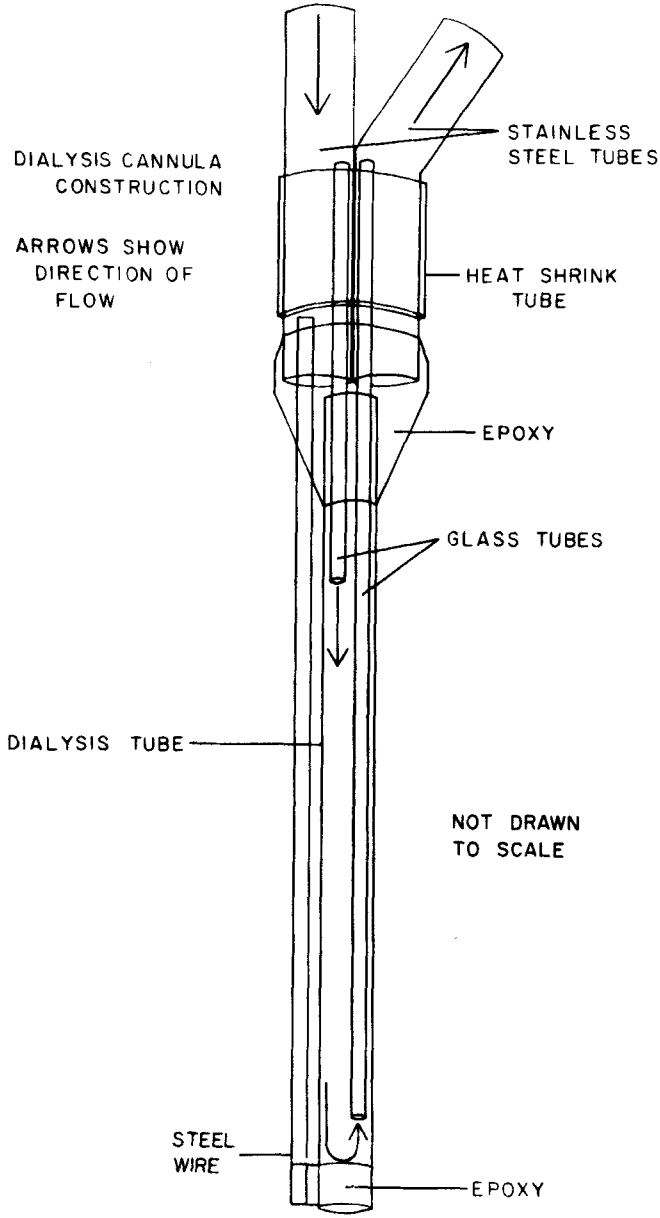

FIGURE 2. Details of the dialysis cannula. Diameter of the cannula is about 200 micrometers. The length depends upon the structure to be perfused. The six pin connector which surrounds the top of the cannula is not shown.

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sealed at one end with a cyano-acrylate adhesive. Glass tubing of 2 mm diameter is then pulled over a flame to make glass capillaries of less than 100 um diameter. One length of this is inserted into the sealed dialysis tubing to approximately 0.5 mm from the sealed end. A second glass capillary is inserted to 6 mm above the end of the first. The two glass capillaries are then trimmed to extend about 7 mm from the open end of the dialysis tube. To connect the dialysis cannula to the flexible tubing coming from the fluid swivel at the top of the test chamber, 23 gauge stainless steel tubing is cut into two pieces approximately 15 mm in length. One tube is bent at a slight angle about 4 mm from one end to make attachment of the tubing from the swivel easier. The two tubes are then held together with 24 gauge heat-shrinkable teflon tubing, making sure that the bottom ends of the two tubes are flush with each other. The ends of the glass capillaries are then inserted into the flush ends of the stainless steel tubing. This junction is sealed with cyano-acrylate adhesive. In order to reinforce the rather flexible dialysis cannula, a length of fine (0.012 inch) wire 26 mm long is attached at the tip of the cannula and at the junction of the stainless steel tubes. To provide for secure attachment and accurate placement of the cannula, the dialysis cannula is mounted in the center of six pin male connector (Plastic Products, Roanoke, VA.) which has been drilled out in the center to hold the cannula. This connector mates with a six pin female

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connector secured to the skull. The female connector contains a central 20 gauge stainless steel guide cannula 15.3 mm long which extends just below the dura.

Dialysis Perfusion Procedure

Male Sprague Dawley rats (Harlan Laboratories) are used in all experiments. Rats are implanted with a cannula guide described above using standard stereotaxic procedures. The lower end of the guide is placed at the following coordinates: AP 8.6, Lat 2.5, height 0.5 mm below dura(12).

After all instrumentation has been turned on and a steady chromatographic baseline achieved, standards of DOPAC, HVA, 5-HIAA (10 ng/100 ul) and AA (100 ng/100 ul) are injected for calibration. Peak heights of samples are compared to peak heights of standards for quantitation. After chromatography of the standards the syringes of the perfusion pump are filled with artificial CSF and the lines checked for air bubbles. The dialysis cannula, which has been previously checked for leaks, is attached to the two lines of the perfusion pump. Before the dialysis cannula is placed in the brain, the animal is lightly anaesthetized with ether to prevent breakage of the cannula during insertion. After the cannula has been inserted and locked in place, the perfusion pump is started at 4 ul/min. The first perfusate injection is made 40 minutes after the start of perfusion, by which time the animal has visibly recovered from

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anesthesia. This also allows time for the perfusate to travel to and fill the sample loop. After the first injection, perfusate is injected every thirty minutes.

The first three hours of sampling are used to obtain a baseline. Subsequently, pharmacological or behavioral stimuli are introduced. For the pharmacological experiments, animals are either given the drug of interest or saline. The samples continue to be chromatographed every thirty minutes for the duration of the experiment. At the termination of the experiment, the push-pull lines are disconnected from the cannula, the dialysis cannula is gently removed and the animal is returned to its home cage. The dialysis cannula is examined and the system is cleaned with distilled water. Histology is subsequently done to verify cannula placement.

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Chromatography

A Waters model 6000 solvent delivery system is used with a Rheodyne 7010 injection valve. A 100 ul sample loop is used for sample introduction. The detector is an LC-3 amperometric detector from Bioanalytical Systems with a glassy carbon working electrode set at a potential of +0.75 V vs. Ag/AgCl. Peak heights are measured on a Fisher Recordall 5000 strip chart recorder set a 1 V full scale for the neurotransmitter metabolites while the ascorbic acid peak height is measured on a McKee-Pederson recorder set at 10 V full scale.

The analytical column is a 4.6 mm by 25 cm stainless steel 10 um Zorbax C8 reverse phase column (DuPont, Wilmington, DE). The analyses are done at ambient temperature with isocratic elution using a 0.05 M phosphate buffer at pH 4.0, containing 3 percent methanol. The mobile phase is prepared by dissolving 6.9 grams sodium phosphate monobasic in 970 ml distilled water. Thirty ml of methanol are then added and the resulting solution is adjusted to pH 4 with 6N HCl. The eluent is filtered through a 0.45 um filter before use and is degassed vigorously with helium for approximately 15 minutes prior to use and slowly during the chromatography. The eluent flow rate is 1.6 ml/min.

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MATERIALS

All chemicals were purchased from Aldrich (Milwaukee, WI) except for haloperidol (Haldol, MacNeil Laboratories) and d-amphetamine sulfate (Sigma).

Stock solutions of DOPAC, HVA and 5-HIAA were prepared in 0.01 M HCl containing 0.1 percent sodium metabisulfite as an antioxidant. Standard solutions (10 ng/100 ul) were made from these stocks in artificial CSF on the day of the analysis. The ascorbic acid stock was made up fresh each day in artificial CSF at a concentration of 100 ng/ 100 ul.

The artificial CSF was made by adding 7.46 g NaCl, 0.190 g KCl, 0.140 g $CaCl_2$, and 0.189 g $MgCl_2$ to one liter distilled water, as described in (13).

RESULTS AND DISCUSSION

The system illustrated in Figure 1 was built to provide additional information to aid in the interpretation of in vivo voltammetric data. Several approaches to the problem of interpretation of voltammetric data obtained in brain tissue have been used, including differential pulse voltammetry and semidifferential pulse voltammetry(14,15,16). We have taken a different approach in which the extracellular fluid of the striatum is sampled for chromatographic analysis. This allows us to determine which electroactive compounds in the extracellular fluid of the striatum contribute to the changes in oxidation currents observed following the administration of various drugs and during certain behaviors such as feeding. The results reported here concern the initial period of sampling and the drugs amphetamine and haloperidol.

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The dialysis/chromatography system illustrated in Figure 1 has several advantages for analysis of extracellular fluid. The chromatography is aided because the sample is prepurified of any protein which could degrade column performance. This allows elimination of protein precipitating agents which obscure early eluting compounds such as ascorbic acid. Removal of protein very early in the sampling process also eliminates enzymatic degradation of compounds in the perfusate. In addition, tissue damage is minimized because the fluid flow and associated turbulence are contained within the dialysis tube. Because slow

flow rates can be used, and the device has a relatively large surface area, recoveries are high. Dialyzed perfusion has been shown to be suitable for analysis of amino acids and for monitoring dopamine release in freely moving rats (17,18).

One of the main difficulties in the analysis, aside from the difficulty in obtaining samples, was finding chromatographic conditions which would resolve all the compounds of interest. While suitable conditions could be found for the neurotransmitter metabolites, ascorbic acid was obscured by protein precipitating agents such as perchloric acid which eluted in the solvent front. Conditions which were suitable for ascorbic acid (19) were inappropriate for the other compounds. Accordingly, in the initial studies on the effect of amphetamine, the sampled fluid was analyzed for ascorbic acid in one set of experiments (20) and for the neurotransmitters and metabolites in another series(21). Later, with the on-line analysis, it became possible to determine the compounds of interest with one set of chromatographic conditions, as illustrated in Figure 3. The on-line system meant that protein precipitants could be eliminated from the sample.

A consistent observation of in vivo voltammetry is the decline in oxidation current from the initial measurement to some steady state baseline after a series of measurements. Figure 4 illustrates this phenomena for four separate recordings from the same electrode every other day over an eight day period. These data were obtained using a one second chronoamperometric pulse of

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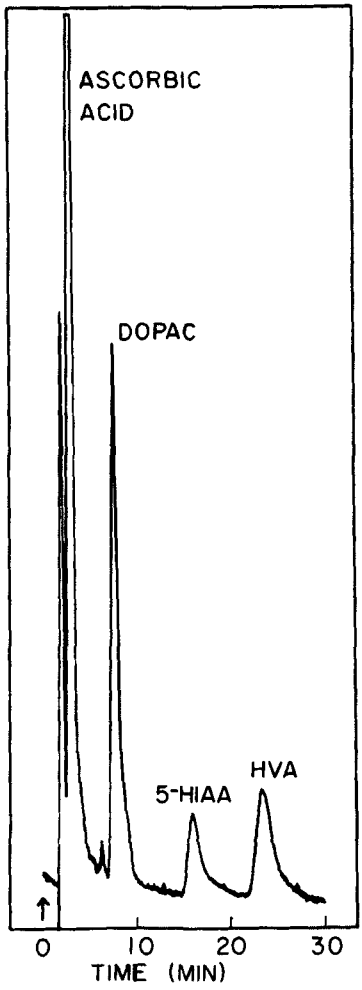

FIGURE 3. Chromatogram of dialyzed perfusate from anterior striatum. Working electrode potential at +0.75 V vs. Ag/AgCl. Mobile phase is pH 4.0 phosphate buffer with 3 percent methanol at a flow rate 1.6 ml/min. The stationary phase is 10 um Zorbax C8 reverse phase in a 4.6 mm by 25 cm stainless steel column.

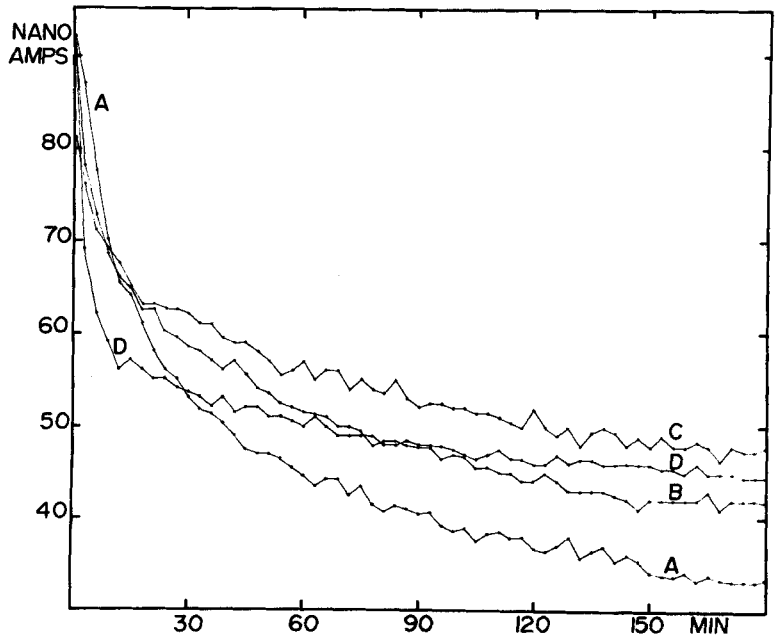

FIGURE 4. Chronoamperometric recordings from anterior striatum of unanesthetized, freely moving rat. Oxidation currents obtained at 100 um carbon epoxy electrodes using one second pulses of +0.6 V vs. Ag/AgCl at three minute intervals. Recordings obtained every other day in order A,B,C,D.

+0.6 V vs. Ag/AgCl every three minutes with a 100 um diameter carbon-epoxy electrode in the anterior striatum of a freely moving unanaesthetized rat. In each case the oxidation current became progressively smaller until a steady state was established. A model has been proposed to account for these observations(22) in which a small "pool" of extracellular fluid surrounds the electrode tip. As the oxidation at the electrode

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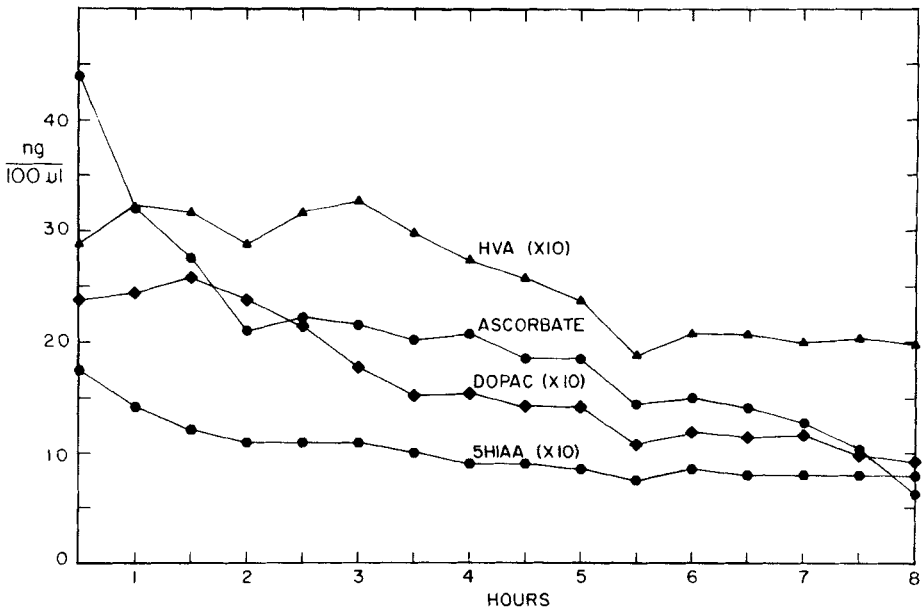

FIGURE 5. Time course of extracellular ascorbic acid, DOPAC, HVA, and 5-HIAA from anterior striatum of unanesthetized, freely moving rat. Samples obtained by dialysed perfusion at 4 ul/min. The data are expressed per 100 ul sample.

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surface lowers the concentration in this pool, the current becomes progressively smaller and a concentration gradient is established with respect to the surrounding tissue. Eventually, as material flows into the pool as a result of the gradient, a steady state is reached in which consumption at the electrode surface is equalled by influx from the surrounding tissue. The model has been modified(23) to include differences in mass transfer rates for different molecular species. This latter model seems more appropriate as the data of Figure 5 suggest.

The data in this figure were collected during dialyzed perfusion of the anterior striatum of the rat as described in the methods section.

While dialyzed perfusion does not offer the sampling rate of voltammetry, it permits the resolution of the various electroactive components of the extracellular fluid. Thus Figure 5 illustrates the time course of extracellular levels of ascorbic acid, the dopamine metabolites DOPAC and HVA, and the serotonin metabolite 5-HIAA over an eight hour period from the start of perfusion for an N of seven. The interesting observation here is that ascorbic acid is behaving differently from the neurotransmitter metabolites. While the neurotransmitter metabolites appear to be unaffected by the perfusion, there is a considerable decrease in the initial ascorbic acid level to a steady state baseline. This implies that the extracellular level of ascorbic acid is more seriously affected by the sampling method. It may be that the neurotransmitter metabolites are part of a process with a high turnover rate relative to the rate of removal by voltammetry or perfusion and are therefore unaffected by the sampling process, while ascorbic acid has a much slower turnover rate so that the extracellular "pool" of ascorbic acid in the vicinity of the sampling device is apparently seriously affected by the sampling process. This interpretation of course requires additional data before it or any other interpretation can be said to explain the difference.

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Using the relative concentrations of the electroactive species present in the extracellular fluid and their change over time, it is possible to predict the change in oxidation current of an electrode in response to changing extracellular concentrations. The additional information needed to calculate such a curve is the relative response of these compounds at a given electrode type. The general form of the equation for the relative oxidation current at time t is:

$$i(t) = \sum (\text{relative response} \times \text{relative concentration}(t))$$

for all compounds electroactive at the applied potential. For a carbon-epoxy electrode and a potential of +0.6 V vs. Ag/AgCl, this equation becomes:

$$i(t) = 0.40(AA(t)) + 1.0(DOPAC(t)) + 0.53(HVA(t)) + 0.85(5\text{-}HIAA(t))$$

where i(t) is the relative current rather than the absolute current, and the abbreviations in parentheses represent relative concentrations. The coefficients were determined by chronoamperometry of 1.0 mM solutions of each component in physiological saline (pH 7.4). To determine the relative concentrations, the nanograms of each component from each 100 ul

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sample were converted to a percent of the baseline for each component. These percentages are then multiplied by the baseline amount of the components to account for the quantities of the components relative to each other. Calculation of an absolute current would require absolute extracellular concentrations, the active area of the electrode and diffusion coefficients in the extracellular matrix.

A comparison of calculated and observed voltammetric data for the initial period of decreasing response is shown in Figure 6. The observed voltammetric data are the four curves of Figure 4, averaged and grouped into periods of fifteen minutes. The data for both the calculated and observed cases are expressed as a percent of the baseline obtained from the three points at the end of each curve. The agreement is surprisingly good given that two different sampling processes are being used. This agreement supports the suggestion that ascorbic acid is the principal source of the initial decline in oxidation current.

The dialysis/perfusion process is analogous to voltammetry in that material is removed, although the rates of removal and geometries are different. An additional difference is that the dialysis/perfusion process removes all compounds with a molecular weight less than the cutoff for the membrane, while the electrode removes only compounds oxidizing at the applied potential. A comparison of the two sampling processes may be made using the geometry and rate of removal for each process. A

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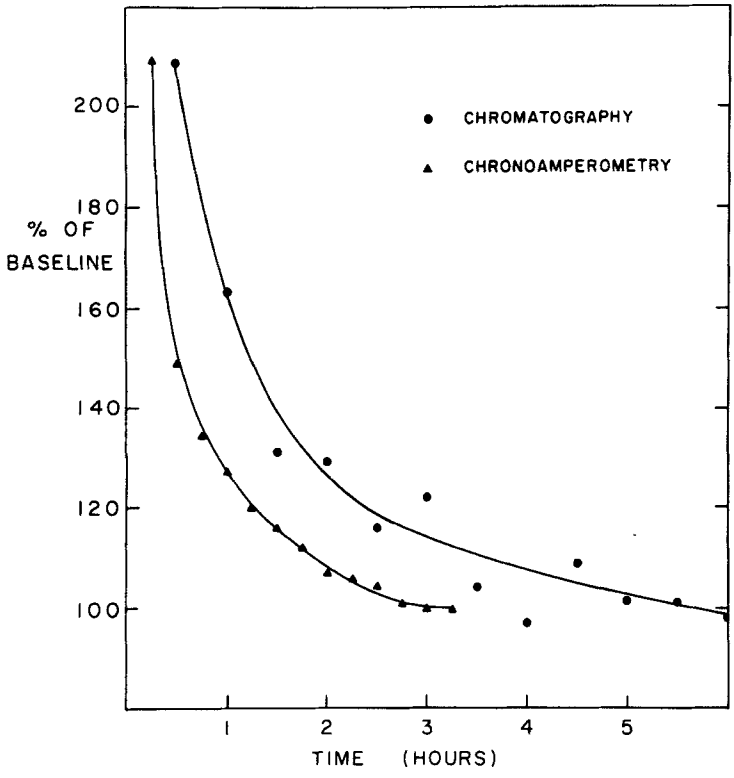

FIGURE 6. Comparison of calculated and observed change in oxidation current during initial period of voltammetry and perfusion. Data are expressed as a percent of the baseline for each curve.

100 um diameter electrode has a geometric surface area of 0.0008 mm^2 while a dialysis cannula 4 mm long has an area of 2.5 mm^2. The electrode of Figure 4 has about a 45 nA baseline current for one second chronoamperometry every three minutes. This corresponds to about 0.07 pmoles/min for a two electron oxidation, or 9 pmoles/min/mm^2. For the dialysis cannula, about 2 pmoles/min/mm^2 of ascorbic acid are being removed, with

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correspondingly smaller amounts of the neurotransmitter metabolites. Thus the rate of removal per unit area is higher for the electrode than the dialysis cannula. These approximate calculations may help to explain why the observed voltammetric curve decreases more rapidly than the voltammetric curve calculated from the dialysis data.

A calculation similar to that for the initial decrease in current can also be done for the effect of drugs on extracellular levels of electroactive compounds. Haloperidol is a dopamine receptor blocker which leads to increased release of dopamine that in turn increases the level of dopamine metabolites. A 1.0 mg/kg dose i. p. generates the voltammetric curve shown in Figure 7. The data were obtained using chronoamperometry at +0.5 v vs. Ag/AgCl at a carbon paste electrode with one second pulses every one minute in the anterior striatum of anaesthetized rats. Previous work in this laboratory using dialyzed perfusion of the anterior striatum of unanaesthetized rats during a 1.0 mg/kg injection of haloperidol(i. p.) has demonstrated that the dopamine metabolites DOPAC and HVA increase by 226 percent as a result while ascorbic acid and the serotonin metabolite 5-HIAA do not increase(24). Dopamine and serotonin were not detectable under the conditions used and therefore probably does not contribute significantly to the change in oxidation current for this particular pharmacological treatment. The equation for the expected change in oxidation current is:

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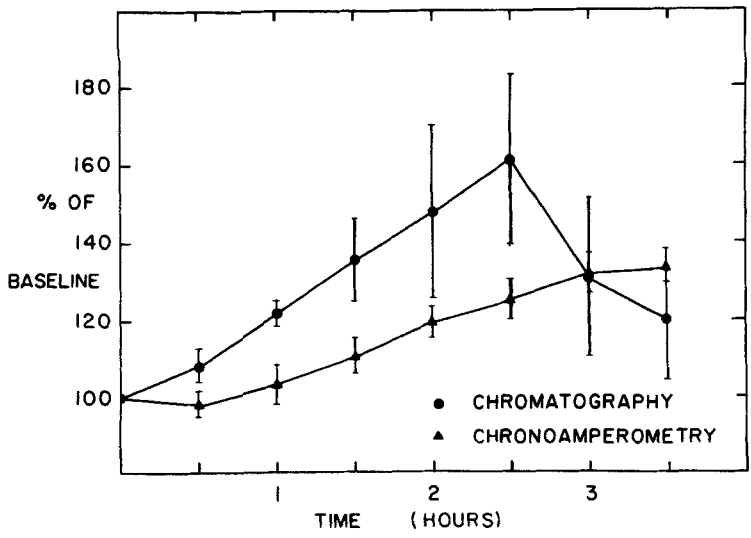

FIGURE 7. Comparison of calculated and observed change in oxidation current following administration(i.p.) of 1.0 mg/kg haloperidol. Three hour baseline preceded drug administration. Chronoamperometry performed with a carbon paste electrode at +0.5 V vs. Ag/AgCl for one second at one minute intervals.

$$i(t) = 0.40(AA(t)) + 1.0(DOPAC(t)) + 0.24(HVA(t)) + 0.72(5\text{-}HIAA(t))$$

where the coefficients are based on chronoamperometry of 1.0 mM solutions of each compound in physiological saline with a carbon paste electrode at +0.5 V vs Ag/AgCl. The perfusion data of Blakely et al.(24), when used in the above equation yield the results of Figure 7. It can be seen that the calculated increase is greater than but similar to the observed increase. The lower increase for the observed voltammetric data may be due to the effect of the anaesthesia.

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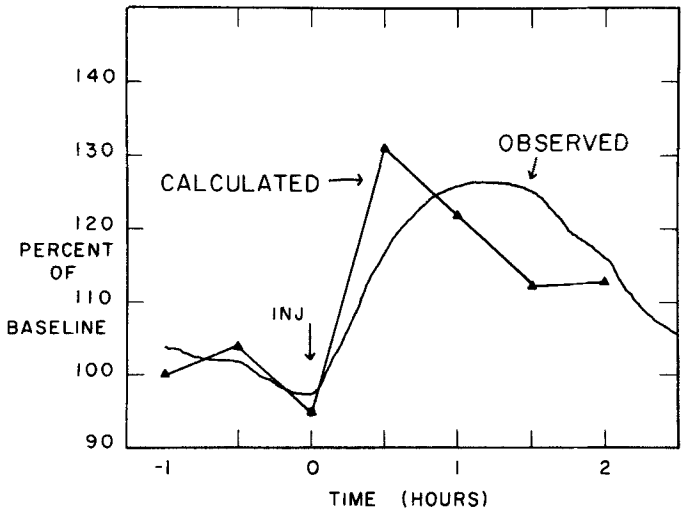

FIGURE 8. Comparison of calculated and observed change in oxidation current following i.p. administration of 1.0 mg/kg amphetamine. Data expressed as percent of baseline. Chronoamperometry done at +0.6 V vs. Ag/AgCl for 1 second at three minute intervals with a carbon-epoxy electrode. Chronoamperometric data collected for 3 hours before administration of 1 mg/Kg d-amphetamine sulfate. All data obtained in anterior striatum.

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Amphetamine has been the source of considerable confusion with respect to the changes it causes in extracellular levels of electroactive compounds in the brain. The various voltammetric results have been reviewed by Adams and Marsden(10). Chromatographic data obtained previously with conventional push pull cannulae which demonstrated that amphetamine increases extracellular ascorbic acid in the striatum(20) and that it decreases extracellular DOPAC and HVA (21). A calculation of the expected change in oxidation current can be made from these data.

The results of this calculation are shown in Figure 8, where the calculated change from baseline is superimposed on the observed change in oxidation current. Because the push pull data were obtained from two separate cannulae (and therefore at possibly different exchange rates) and because 5-HIAA was not measured, it is, as with Samuel Johnson's dog, remarkable not that the data agree reasonably well, but that they agree at all. These data support the observations of Dayton et al.(16) and Gonon et al.(6,9).

These experiments demonstrate that different electroactive components of the extracellular fluid are contributing to alterations in the voltammetric signals under different stimulus conditions. They also indicate that in vivo voltammetry can be used to monitor these alterations if independent experiments to interpret the changes in the oxidation currents are conducted.

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