Review

Application of Microdialysis in Pharmacokinetic Studies

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The objective of this review is to survey the recent literature regarding the various applications of microdialysis in pharmacokinetics. Microdialysis is a relatively new technique for sampling tissue extracellular fluid that is gaining popularity in pharmacokinetic and pharmacodynamic studies, both in experimental animals and humans. The first part of this review discusses various aspects of the technique with regard to its use in pharmacokinetic studies, such as: quantitation of the microdialysis probe relative recovery, interfacing the sampling technique with analytical instrumentation, and consideration of repeated procedures using the microdialysis probe. The remainder of the review is devoted to a survey of the recent literature concerning pharmacokinetic studies that apply the microdialysis sampling technique. While the majority of the pharmacokinetic studies that have utilized microdialysis have been done in the central nervous system, a growing number of applications are being found in a variety of peripheral tissue types, e.g., skin, muscle, adipose, eye, lung, liver, and blood, and these are considered as well. Given the rising interest in this technique, and the ongoing attempts to adapt it to pharmacokinetic studies, it is clear that microdialysis sampling will have an important place in studying drug disposition and metabolism.

KEY WORDS: microdialysis sampling; pharmacokinetics; drug distribution; probe recovery; blood-brain barrier; extracellular fluid.

INTRODUCTION

The technique of in vivo microdialysis has become one of the major research tools in experimental neurophysiology and neurochemistry. The large body of work published over the past three decades in this field underscores the importance of microdialysis, primarily in providing needed information concerning neurotransmitter release, uptake and metabolism.

Recently, in vivo microdialysis has found important applications in the field of pharmacokinetics, especially in the area of drug distribution and metabolism. This has been made possible by refinements and improvements in the quantitative aspects of the methodology, primarily those which characterize microdialytic recovery.

Principle of Microdialysis

Microdialysis involves perfusion of a microdialysis probe implanted in tissue (e.g., brain or peripheral tissues) under nonequilibrium conditions, i.e., the effluent concentration of analyte is less than that surrounding the probe membrane (see Figure 1). Therefore, dialysate concentrations of the solute or analyte of interest (Ces, the concentration of the solute in the effluent) are a fraction of the concentration in the extracellular space (Cos, the concentration of the solute outside of the probe in the extracellular fluid (ECF)). Knowledge of the fractional recovery (the ratio of the dialysate concentration to that in the extracellular fluid surrounding the probe membrane, Ces/Cos) of the solute or analyte is a prerequisite for calculating tissue extracellular concentrations of the analyte.

During perfusion of a dialysis probe, the driving force for solute movement is diffusion along the concentration gradient between two regions which are separated by a semi-permeable membrane. In vivo, these regions or spaces represent the tissue extracellular fluid (ECF) and the perfusing solution inside the microdialysis probe. Diffusion occurs through a polymeric membrane which encloses the tip of the dialysis probe. Endogenous compounds (e.g., hormones, neurotransmitters) and exogenous compounds (drugs and their metabolites) diffuse in, whereas compounds which have been added to the perfusate (e.g., the perfusate inflow concentration of a "calibrator" is represented by Cic in Figure 1), diffuse out from the perfusion solution. The technique is therefore used not only to continuously monitor the extracellular fluid concentration of analytes, but may also be used to deliver drugs to a specific tissue region. In essence, the principle of the microdialysis technique is to create an "artificial blood vessel" where diffusion of compounds will flow in the direction of lowest concentration.

There are basically three types of probes have been used in microdialysis: the loop probe, the concentric probe, and the linear probe. Although all three probe types have been used widely in neurochemistry and in experiments which have focused on endogenous compounds, much of the recent work in the field of pharmacokinetics has made use of the concentric probe design (see Figure 2). A cylindrical piece of dialysis tubing, which serves as the dialysis membrane, is sealed with
Fig. 1. Microenvironment within and surrounding the microdialysis probe in vivo (not drawn to scale). The solid and dashed line segments schematically represent the nonpermeable probe wall and semipermeable membrane, respectively. Open and closed circles represent the molecules of the solute of interest and a retrodialysis calibrator, respectively. Squares and triangles represent macromolecules which may bind solute and/or calibrator, but which are not recovered by the dialysis process. Arrows indicate direction of mass transport. Abbreviations are as defined in the text.

an adhesive at one end and the other end is fixed to the lip of the outer shaft. A thin inner cannula, usually made of metal or fused silica, extends through the outer shaft and dialysis membrane, almost to its sealed tip. Perfusate solution enters the proximal end of the inner cannula and flows distally all the way to the end of the membrane where it is sealed. Every attempt is made to minimize the dead volume of the probe (the volume contained from the membrane to the outlet) to reduce the lag time associated with dialysate measurements in relation to the concentration in the ECF. The dialysis membrane material should be biocompatible and inert. The average pore size should be large enough to allow free diffusion of solute molecules, but small enough to restrict the passage of proteins and other macromolecules. Several different types of semipermeable membranes have been employed, including: polycarbonate-ether, regenerated cellulose, and polyacrylonitrile (PAN) (1). Recently, a polyether sulfone (PES) membrane has been introduced with a greater molecular weight cutoff (100,000 daltons) than most other membranes (ca. 5,000 to 30,000 dalton MWCO). This material may make the microdialysis sampling of larger molecules feasible, opening new areas of application.

Fig. 2. Schematic representation of solute recovery in vivo and in vitro (not drawn to scale). See text for definition of terms.