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Review

Clinical microdialysis in neuro-oncology: principles and applications

J. Clay Goodman

Abstract

Clinical microdialysis allows a discrete volume of the brain to be sampled for neurochemical analysis of neurotransmitters, metabolites, biomarkers, and drugs. The technique can be safely used in humans intraoperatively, in the intensive care unit, and in ambulatory settings. Microdialysis probes, micropumps, and analytical equipment are commercially available and have been used extensively for neurochemical monitoring in traumatic brain injury, stroke, and subarachnoid hemorrhage. There has been very limited use of microdialysis in neuro-oncology, but this technique has great promise in the study of the basic neurochemistry of brain tumors, alterations in neurochemistry in response to therapy, and the pharmacokinetics of chemotherapeutic agents. Microdialysis probes may also be used to deliver drugs while simultaneously permitting monitoring of neurochemical changes induced by this therapy.

Key words Microdialysis, neurochemistry, neuro-oncology, pharmacokinetics

Microdialysis, an experimental technique for sampling the neurochemical milieu of a local region of the brain, was developed and validated in animals in the 1970s and first entered clinical application in the early 1990s. Since that time, numerous centers around the world have used microdialysis in clinical settings. Because the technique is invasive, it has been used primarily intraoperatively or in a neurological intensive care setting, but technical advances now permit use of microdialysis in ambulatory patients in a more chronic setting. The technique has been used in traumatic brain injury, ischemic stroke, subarachnoid hemorrhage, epilepsy, and Parkinson's disease. Traumatic brain injury and stroke have been studied most extensively, and the basic principles, analytes, and technology are well-established and readily available for translation to other areas of clinical neuroscience, including neuro-oncology. There are several excellent recent reviews of the basic principles and clinical application of microdialysis[1-6].

Microdialysis has been used to a very limited extent in experimental neuro-oncology and even less in patients with brain tumors[7-9]. This is due to the short duration of stays for brain tumor patients in intensive care units, as well as concerns about the safety of placing microdialysis probes in tumor beds. Nevertheless, recent developments in microdialysis instrumentation may make the technique more readily applicable to ambulatory patients. Furthermore, the studies performed to date in patients with brain tumors indicate that microdialysis probes can be safely placed.

This article will review the principles of cerebral microdialysis, briefly examine the analytes that have gained cache in neurocritical care, and then discuss in detail its possible applications in neuro-oncology. Microdialysis has substantial potential to provide information about the biochemical milieu of the native brain tumor, therapy-induced changes in the tumor neurochemical environment, and insight into the neuro-pharmacokinetics of brain tumor drugs.

Principles of Cerebral Microdialysis

Cerebral microdialysis uses an implanted probe that interacts with the brain's extracellular space by diffusion. More specifically, a microdialysate perfusate solution, which is similar in composition to cerebrospinal fluid, is pumped through the implanted probe, allowing diffusion of molecules from the extracellular space through the probe's semi-permeable walls. The perfusate containing these molecules is then collected for analysis at the bedside or at a remote analytical laboratory (Figure 1). The current generation probe consists of a piece of tubing surrounded by a sleeve of rigid semi-permeable membrane mounted on a rigid base that can be attached to the skull. There is an inflow port through which perfusate is slowly pumped. The perfusate travels the

Author's Affiliation: Department of Pathology & Immunology, Baylor College of Medicine, Houston, TX 77030, USA.

Corresponding Author: J. Clay Goodman, Department of Pathology & Immunology, Room 286A MS: BCM315, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Tel: +1-713-798-7234; Email: jgoodman@bcm.edu.

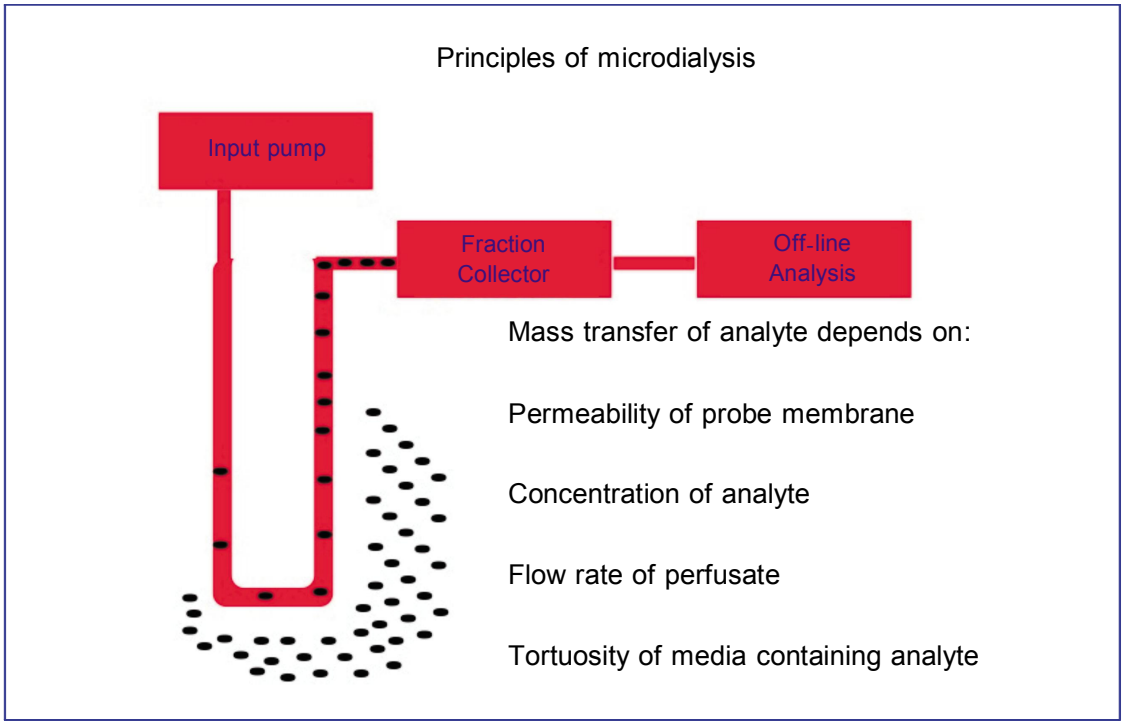

Figure 1. The basic principles of cerebral microdialysis. Artificial cerebrospinal fluid is slowly pumped into the microdialysis probe using a microsyringe pump capable of pumping very low volumes of fluid. The wall of the probe is semi-permeable to small molecules which diffuse from the extracellular space of the brain into the dialysate fluid. The analyte molecules must diffuse through the extracellular space, but their diffusion pathways are geometrically complex; the tortuosity of the extracellular space can restrict diffusion. Ultimately, the amount of analyte that is collected for analysis depends on the permeability of the probe's membrane, the concentration of the analyte, the flow rate of the perfusate, and the tortuosity of the extracellular space.

length of the probe and is then collected by a centrally located outflow tube (Figure 2). To begin the procedure, a microsyringe slowly pumps the perfusate into the inflow port of the probe, and the solution flows distally through the length of the probe. Solutes within the perfusate diffuse from the perfusion solution to the brain tissue interstitium, but, more importantly, molecules from the extracellular fluid diffuse into the probe. If the perfusion rate is sufficiently slow, the analytes reach concentration equilibrium between the perfusate and the extracellular space of the brain. The equilibrated solution containing the analyte of interest is collected at 30 to 60 min intervals from the centrally located outflow tube and analyzed at the bedside or in the laboratory (Figure 2).

Analyte recovery is determined by perfusion rates, probe permeability, and tissue tortuosity. In the early days of this technique, perfusion rates were 3 μL/min, which was too fast for equilibrium to be established across the microdialysis probe membrane. As a result, the concentration of analyte in the dialysate was usually less than the concentration surrounding the probe membrane. The fractional recovery, the ratio between the concentration of analyte in the perfusate and in the extracellular space, provided an indirect measure of the concentration within the extracellular space. With a perfusion rate of 3.0 μL/min, the fractional recovery was usually between 30% and 60%. In the last ten years, however, technical advances have resulted in the typical perfusion rate being 0.3 μL/min and a fractional recovery of 100%. Portable, low-volume micropumps that can be worn by ambulatory patients are now commercially available, making microdialysis studies possible in ambulatory patients. In addition to perfusate flow rate, the analyte recovery is also determined by the permeability properties of the probe membrane. Most probes have a molecular weight cut-off of 20 to 30 ku although probes with a molecular weight cut-off of 100 ku are now available. Probes permeable to low-weight molecules are entirely satisfactory for the study of most drugs, small metabolites, and some small proteins. Analyte recovery is further influenced by the ease with which the analyte diffuses in the extracellular space. The extracellular space comprises approximately 15% of the brain volume, but this space is geometrically very complex. This geometric complexity is expressed quantitatively by a biophysical property called tortuosity (Figure 3). The greater the tortuosity, the more diffusion is impeded and the lower the analyte recovery. The

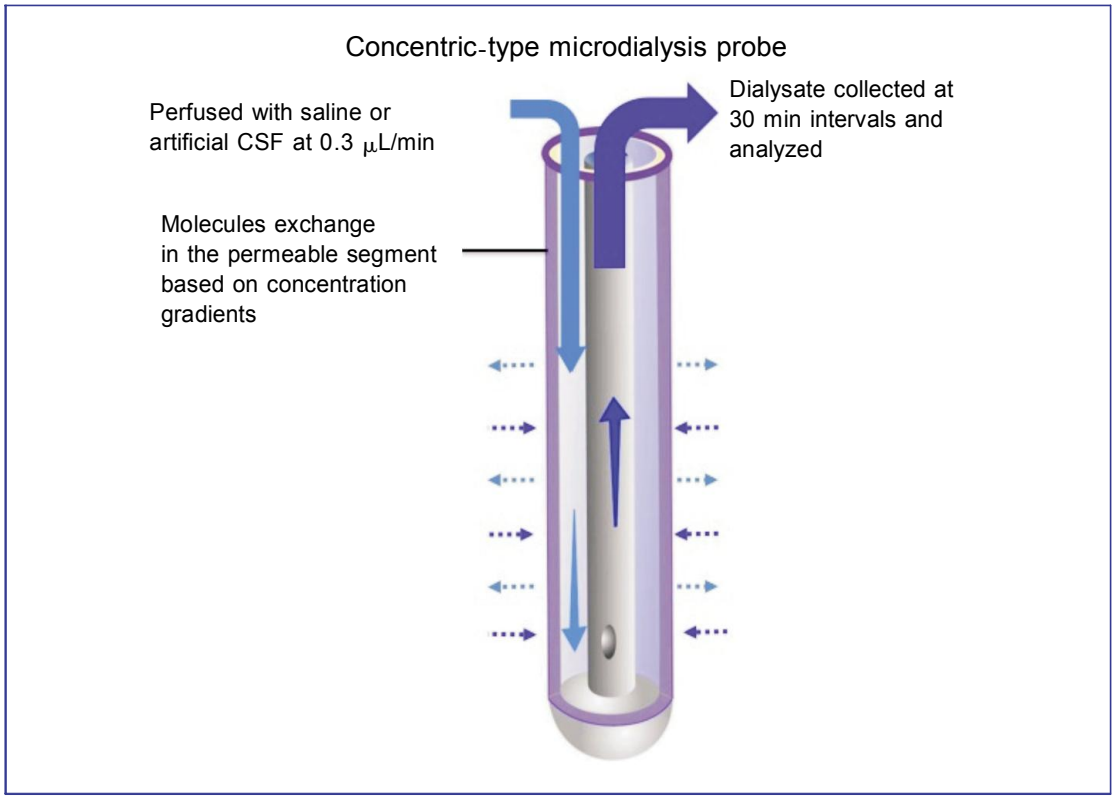

Figure 2. Current generation microdialysis probes have concentrically arranged tubing. The outer tube is composed of a rigid semi-permeable membrane. The perfusate is pumped into this space, where equilibration with the extracellular space of the brain occurs. After equilibration, the perfusate fluid, now containing analytes, is collected in a centrally located tube, which stores the fluid for later collection and analysis. (Modified from Dr. Urban Ungerstedt with permission)

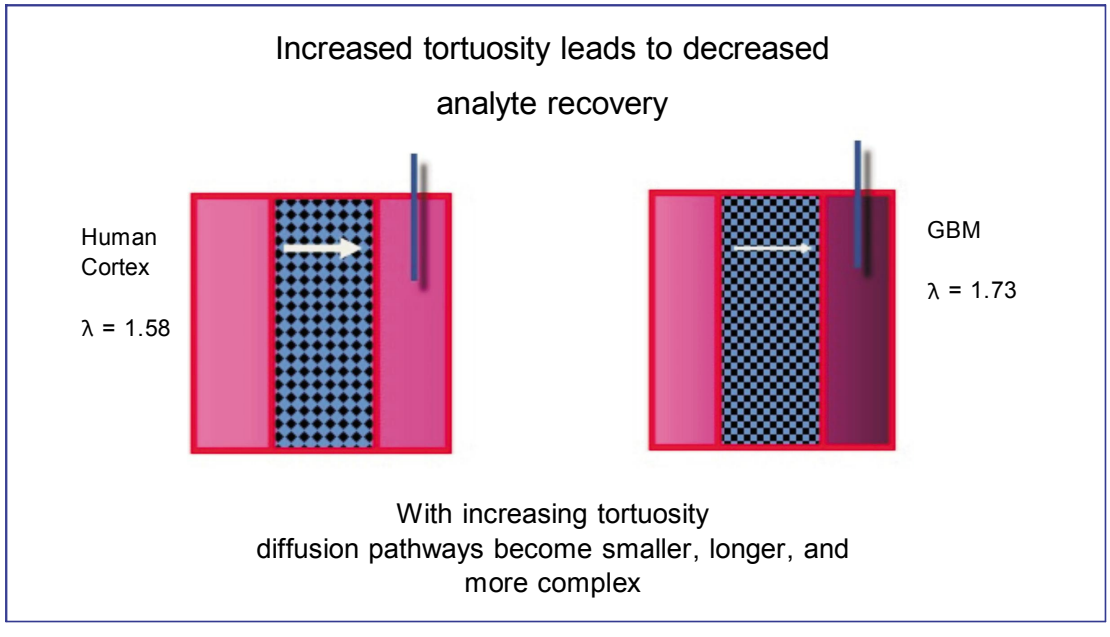

Figure 3. The complex geometry of the extracellular space restricts diffusion of analytes to the probe. The degree of restriction of diffusion can be measured and expressed mathematically as the tissue tortuosity. Measurements in glioblastoma multiforme generally show greater tortuosity which restricts diffusion; therefore, apparent analyte concentrations will be lower in tumor than in normal brain.

tortuosity in pathological states like tumors is different than in normal brain, so direct comparisons of analyte concentrations in normal and abnormal brains must be approached with some caution.

Commonly Measured Analytes and What They Mean

Several analytes are widely used in clinical microdialysis. These compounds are biochemical signatures of the structural and functional state of the neuropil adjacent to the probe. To be used for clinical monitoring, an analyte must be reasonably stable and the analytical method must be straightforward and applicable to the very small volumes of dialysate. Currently, bedside collection and analysis of glucose, lactate, glutamate, and glycerol is possible using commercially available instrumentation (CMA Microdialysis AB, Solna, Sweden). More exotic analytes, such as cytokines, free radicals, nitrate and nitrite, or drugs, can be collected and assayed off-line at the leisure of the analytical laboratory (Figure 4).

Glucose and lactate are commonly used to assess the bioenergetic state of the brain, whether physiological aerobic or anaerobic metabolism is occurring. Physiological levels for glucose and lactate are established; thus, alterations in these levels provide useful biochemical information. An increase in lactate and decrease in glucose, for example, indicates a state of bioenergetic crisis wherein anaerobic metabolism is active. The lactate/glucose ratio is often used to express the metabolic state of the neural tissue, with high ratios corresponding to neurochemical deterioration. The increased reliance of tumors on anaerobic metabolism would likely result in a more anaerobic ratio, making this well-established neurochemical parameter of interest to neuro-oncologists[6,10,11].

Glutamate is the most abundant excitatory amino acid in the mammalian brain. In traumatic brain injury and ischemia, uncontrolled release of this neurotransmitter, which usually follows bioenergetic deterioration, results in excitotoxicity, unregulated activation of ligand-gated channels that induces cellular calcium uptake resulting in caspase activation, mitochondrial quenching, and, ultimately, cell death. Several publications suggest that glutamate is released by infiltrating glioma cells, potentially killing obstructing normal cells and thereby facilitating invasion. Thus, this analyte may also be of interest in neuro-oncological

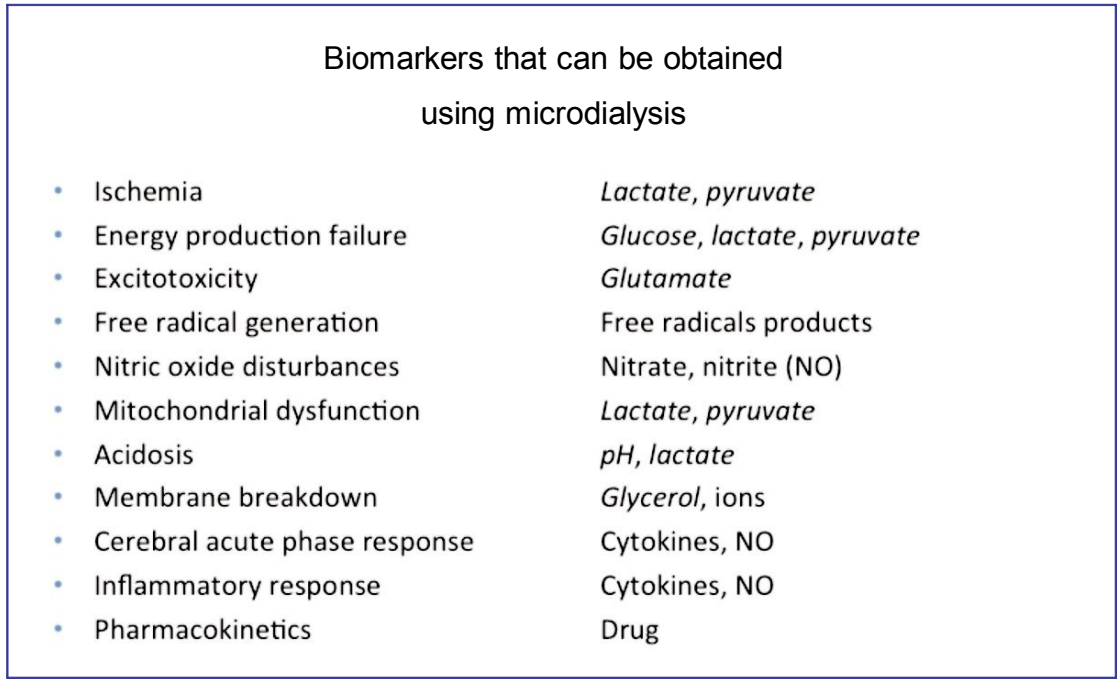

Figure 4. A variety of molecules can be obtained using microdialysis. Specific neurochemical signatures of pathological processes such as ischemia, membrane breakdown, excitotoxicity, and membrane breakdown have been validated, and those indicated in italics can be measured with commercially available analytical equipment.

microdialysis studies[12,13].

Glycerol, the small, three-carbon backbone of the triglycerides residing in the cell membrane, is released upon degradation of the membrane's constituents. Elevations in glycerol level generally follow bioenergetic failure and activation of excitotoxicity, and are, therefore, an indicator of late cellular distress. Because glycerol is a biomarker of membrane dissolution and cell death, it could potentially be an ideal indicator of response to tumor cell-killing therapeutics[6,14].

Application of Microdialysis in Neuro-Oncology

Neurochemistry of brain tumors

Microdialysis permits characterization of the neurochemical milieu within brain tumors. Few studies have been conducted. The results suggest that gliomas have a higher level of anaerobic metabolism than normal brain, may release glutamate into the surrounding neuropil potentially facilitating invasion, and new analytes may be discovered by microdialysis coupled to mass spectroscopy.

Relatively few studies have been performed using microdialysis in patients with brain tumors. Bianchi *et al*.[15] examined extracellular amino acids and choline in the extracellular fluid of human cerebral gliomas. They examined 21 high-grade tumors, including 15 classified as grade IV glioblastoma and 6 as grade III anaplastic astrocytoma or anaplastic oligodendroglioma. The extracellular levels of choline, aspartate, taurine, gamma-aminobutyric acid (GABA), and leucine in grade III tumors were not different from adjacent normal brain, whereas they were significantly increased in grade IV tumors than in normal brain. There was no difference between grade III and grade IV tumors in the concentrations of phenylalanine, isoleucine, tyrosine, valine, and lysine, but the concentrations of choline, aspartate, taurine, GABA, leucine, and glutamate were significantly elevated in glioblastomas than in grade III tumors. The concentration of glutamate was decreased in the glioma tissue of both grades; however, the normal parenchyma adjacent to the tumor showed significant elevation in the extracellular concentration of glutamate. It is possible that this glutamate elevation in adjacent tissue may represent the invasive penumbra of the tumor. The concentrations of choline and the amino acids glutamate, leucine, taurine, and tyrosine showed significant positive correlations with the degree of tumor cell proliferation. The authors reported that seizures, which are relatively common in subjects with gliomas, were a significant confounding variable when the extracellular concentrations of aspartate, glutamate, and GABA were considered. These findings are congruent with a small number of publications reporting neurochemical patterns in patients with epilepsy who underwent simultaneous electrode and microdialysis probe placement prior to seizure surgery[16-19].Seizure foci are associated with increased glutamate and lactate and decreased glucose, which may indicate bioenergetic distress with impaired glutamate cycling.

Melani *et al*.[20] used cerebral microdialysis to examine adenosine concentrations as a marker of glioma purine metabolism. They evaluated adenosine levels in the extracellular fluid of 21 human high-grade gliomas using brain microdialysis techniques coupled to high-performance liquid chromatography. The adenosine concentration was (2.99 ± 0.37) mmol/L in the control tissue and (1.56 ± 0.46) mmol/L in the tumor tissue, which was a significant reduction. They concluded that the adenosine concentrations reached in the tumor tissue were sufficient to stimulate all adenosine receptor subtypes, potentially suppressing local anti-tumor immune responses and affecting glial and endothelial cell proliferation.

Roslin *et al*.[21] studied the metabolism of high-grade astrocytoma in 15 patients using intratumoral microdialysis. Two catheters were implanted, one in the tumor and the other in the peritumoral tissue, during a stereotactic biopsy procedure. The patients were mobilized on the same day as the operation. Microdialysis samples were collected the next day and subsequently analyzed for glucose, lactate, pyruvate, glutamate, and glycerol to establish baseline levels of these analytes. In addition, *in vitro* measurements were performed after the removal of the probes to estimate recovery for the flow rates and catheters used. Glucose levels were lower in the tumor than in the peritumoral tissue, indicating the tumor's high energy demand. Lactate level was significantly higher in tumor tissue, supporting previous reports that high grade astrocytomas, like many tumors, use glycolysis rather than respiration to meet energy demand. The tumors were also classified as necrotic and non-necrotic, according to the radiological findings. The necrotic tumors showed significantly higher levels of glutamate and tended to exhibit higher levels of glycerol than the non-necrotic tumors. These findings may be explained by the release of intracellular glutamate stores and cell-membrane glycerol by cell destruction.

Flannery *et al*.[22] demonstrated that novel analytes can be detected using microdialysis when they measured the cysteine protease cathepsin S in human brain tumors. Extracellular proteases like cathepsin S may facilitate astrocytoma invasion. Microdialysates obtained from human brain tumors *in vivo* were subjected to cathepsin S activity and ELISA assays. Cathepsin S expression was detected by ELISA in 5 out of 10 tumor

microdialysates, while protease activity was detected in 5 out of 11 tumor microdialysates. Cathepsin S expression was also detected in microdialysate from the normal brain tissue. These authors concluded that characterization of the extracellular environment of brain tumors *in vivo* using microdialysis may be a useful tool to identify the protease profile of brain tumors.

In a rather unique study, Lindvall *et al.*[23] investigated whether neurochemical degeneration occurred in post-operative glioma patients during air transport. They examined 4 patients with glioblastoma who received either a biopsy or a craniotomy prior to transport. During these procedures, microdialysis catheters were placed in tumor tissue or brain tissue adjacent to the tumor, as well as in normal cerebral tissue. They analyzed cerebral glucose metabolites (glucose, lactate/pyruvate ratio), glycerol, and glutamate at 5 time points during a 24-hour period that included air transport. They found that there was a small but statistically significant increase in the lactate/pyruvate ratio in normal cerebral tissue after air transport. In tumor tissue, there was a small decrease in glucose and an increase in glutamate. No other significant differences were observed in the cerebral metabolites following air transport. Since only minor differences in levels of cerebral metabolites after air transport were observed compared to a previous fasting sample, the authors concluded that post-operative air transport of patients with brain tumors did not result any major cellular damage or cerebral metabolic changes. Importantly also, they demonstrated the technical feasibility of cerebral microdialysis in a unique and demanding environment.

These studies illustrate the remarkable potential for microdialysis in basic investigation of brain tumor biochemistry. Study of the *in vivo* neurochemistry of brain tumors may facilitate development of new diagnostic and therapeutic possibilities in neuro-oncology.

Changes in neurochemistry of brain tumors in response to therapy

Therapy-related changes in brain tumor neurochemistry can also be analyzed by microdialysis. Only a few studies have been conducted to date and changes in conventional analytes have not been detected in the acute setting, but future studies at later time points might demonstrate neurochemical changes indicative of therapeutic effect. One study using mass spectroscopy to detect novel analytes has shown considerable promise to discover new biomarkers of brain tumor response to therapy.

Tabatabaei *et al.*[24] used microdialysis to study the effects of radiotherapy on metabolism in 13 patients with malignant glioma to determine the levels of glucose, lactate, pyruvate, glutamate, and glycerol in tumor tissue during baseline conditions and to detect any changes in these metabolic markers during radiotherapy. Two microdialysis catheters, one in the tumor and the other in the peritumoral tissue, were implanted during a stereotactic biopsy. Fasting samples were analyzed daily, before and during 5 days of radiotherapy given in 2 Gy fractions. Baseline levels of glucose and pyruvate were significantly lower in tumor than in peritumoral tissue, and the lactate/pyruvate ratio was significantly higher in tumor tissue. In general, the levels of lactate, glutamate, and glycerol were higher in tumor tissue, although these differences were not statistically significant. They could not detect any significant changes during the 5 days of radiotherapy in any of the metabolites analyzed. Radiotherapy up to 10 Gy given in 5 fractions did not influence the glucose metabolism, nor did it induce any acute cytotoxic effect detected by elevated glutamate or glycerol levels. The study confirmed the glycolytic properties of glucose metabolism in malignant glioma, but did not demonstrate the neurochemical signatures of cell death. Furthermore, the study was limited only to 5 days of therapy. Thus, it is possible that more prolonged studies might show more robust neurochemical signatures of cytolysis.

Wibom *et al.*[25] also used stereotactic microdialysis to sample extracellular fluid from patients with glioblastoma before and during the first 5 days of conventional radiotherapy treatment. These investigators, however, used very sophisticated analytical techniques to discover new analytes that might be markers of therapy effects. The microdialysis catheters were implanted in tumor as well as the brain adjacent to tumor. Reference samples were also collected subcutaneously from patients' abdomens. The samples were analyzed by gas chromatography coupled with time-of-flight mass spectrometry, and the acquired data was processed by hierarchical multivariate curve resolution and analyzed with orthogonal partial least-squares. To enable detection of treatment-induced alterations, the data was normalized by individual treatment over time. A total of 151 metabolites were reliably detected, of which 67 were identified. The investigators found distinct metabolic differences between the tumor and the adjacent normal brain. There were also marked differences between the intracranial and subcutaneous samples, indicating that the metabolites detected in the brain did not reflect systemic metabolic events. They also observed systematic metabolic changes induced by radiotherapy in both tumor and normal brain. The metabolite patterns affected by treatment were different between tumor and normal brain, both containing highly discriminating information. If validated, findings such as these may contribute to increased molecular knowledge of basic glioblastoma pathophysiology and raise the possibility of

detecting metabolic marker patterns associated to early treatment response.

Pharmacokinetics

Microdialysis has been used for many years to study pharmacokinetics in animals and humans. A few studies of brain tumor chemotherapy pharmacokinetics in patients have demonstrated the technical feasibility and safety of *in vivo* measurement of temozolamide and methotrexate. Even more exciting is the prospect of direct intratumoral delivery of chemotherapeutic agents using microdialysis. All of the studies are preliminary, however, they illustrate the potential of microdialysis in neuro-oncology.

Boschi *et al.*[26] provide an excellent review of preclinical pharmacokinetic studies using microdialysis. This review covers the technical aspects of microdialysis in mice and includes references to many of the published studies on pharmacokinetics and drug delivery. While microdialysis has been used in rats since the 1970s, the advent of genetically engineered mice considerably extended the power of studies using this technique. Since 1992, when microdialysis first entered the clinical arena, there have been a few studies using microdialysis to deliver drugs and to investigate penetration and kinetics of systemically delivered chemotherapeutic agents.

In 1992, Ronquist *et al.*[27] reported using microdialysis to deliver L-2,4 diaminobutyric acid (DAB), a non-physiological, cationic amino acid with potent anti-tumor activity against human glioma cells *in vitro*, into gliomas in 3 patients. Up to 3 microdialysis probes were implanted in the tumor tissue through small dural incisions, and micropumps delivered buffered isotonic 0.125 mol/L DAB solution at 3 mL/day via the probes. The patients were treated for 14 to 21 days without side effects ascribable to DAB or the microdialysis probes. Massive tumor necrosis occurred as judged by comparison of computed tomography performed before and after DAB treatment. DAB administered in this way was well tolerated and showed promising anti-tumor activity in these patients with inoperable malignant glioma.

In 2006, Bergenheim *et al.*[28] extended this study by examining the *in vivo* metabolic effects of DAB administered by microdialysis in 10 patients with glioblastoma. One or two catheters were implanted in tumor tissue, and 2 reference catheters were implanted in normal brain tissue and subcutaneous abdominal tissue. Tumor catheters were perfused with 80 or 120 mmol/L DAB, and reference catheters were perfused with a Ringer solution at a flow rate of 2 mL/min. Treatment was given for a mean of 9.1 days (range, 5–19 days). The treat ment was well tolerated by the patients except for 2 patients in whom transient brain edema appeared near the probe. No other complications related to the technique were encountered. During treatment, an increase in the extracellular amino acids alanine, glycine, glutamate, aspartate, serine, threonine, and taurine was found, potentially indicating a significant influence on the intracellular pool of free amino acids induced by DAB. No change in glucose metabolism or glycerol was evident. The metabolism in normal brain was unaffected during treatment. These authors concluded that microdialysis is a feasible method for intracerebral administration of drugs to tumor tissue in fully mobilized patients with glioblastoma while simultaneously allowing assessment of the neurochemical effects resulting from the treatment. The elevation of glutamate and taurine may indicate that DAB induced cellular toxicity while the unchanged level of glycerol probably indicates that no direct increase in phospholipase activity or degradation of membrane phospholipids occurred. The neurochemical effects were local and restricted to the tumor compartment. The study was not designed to assess the impact on survival, but the study demonstrated the technical feasibility and safety of microdialysis probe placement and delivery of DAB.

In 2009, Portnow *et al.*[29] reported the feasibility of using intracerebral microdialysis to study the neuro-pharmacokinetics of temozolomide in the brain extracellular compartment following oral administration. At the time of surgical debulking, patients with primary or metastatic brain tumors had a microdialysis catheter placed in peritumoral brain tissue and underwent a computerized tomography scan to confirm the catheter location. Patients received a single oral dose of temozolomide (150 mg/m^2) on the first postoperative day. Serial plasma and microdialysate samples were collected over 24 h, and temozolomide concentrations were measured using tandem mass spectrometry. Nine patients were enrolled, and dialysate and plasma samples were successfully collected from 7 of them. The mean temozolomide areas under the concentration-time curve (AUC) in plasma and brain interstitial space were 17.1 and 2.7 μg/mL × hour, with an average brain interstitium/plasma AUC ratio of 17.8%. The mean peak temozolomide concentration in the brain was (0.6 ± 0.3) μg/mL, and the mean time to reach peak level in the brain was (2.0 ± 0.8) h. The authors concluded that using microdialysis to measure the neuro-pharmacokinetics of systemically administered chemotherapy is safe and feasible. The concentrations of temozolomide in the brain obtained by microdialysis were consistent with published data obtained in preclinical models, as well as from clinical studies of cerebrospinal fluid. The authors suggest that the delayed

time required to achieve maximum temozolomide concentrations in the brain may indicate that therapy protocols could be improved by administering temozolomide 2 to 3 h before radiation.

Also in 2009, Blakeley *et al.*[30] used microdialysis to assess intratumoral drug distribution in patients with recurrent high-grade gliomas treated with methotrexate. Microdialysis catheters were placed during surgery for residual glioma 1 day before methotrexate (MTX) administration at 12 g/m^2 over a 4-hour intravenous infusion. MTX was measured by liquid chromatography/mass spectrometry in plasma and microdialysate during the infusion and for 24 h thereafter. Permeability of the blood brain barrier (BBB) in the tissue in which the microdialysis probe was located was determined by digitally merging brain CT and contrast-enhanced MRI images. The microdialysis probe was located in contrast enhanced tumor in 2 patients and non-enhanced tissue in 2 others. Cerebral drug penetration, as indicated by the ratio of the area under the methotrexate concentration-time curves in brain extracellular fluid and plasma, was considerably greater in contrast-enhanced tumor than in non-enhanced tumor. Nevertheless, methotrexate concentrations in extracellular fluid exceeded the average concentration required to kill 50% of glioma cells *in vitro* at 20 to 26 h in both regions of the tumor.

These studies indicate that microdialysis is potentially a very informative technique for characterizing the intratumoral pharmacokinetics of drugs. In experimental systems and now in a very limited number of patients, mi crodialysis probes have been used to deliver drugs. Any compound in the perfusate will diffuse down that compound's concentration into the extracellular space of the brain; therefore, microdialysis (sometimes called retrodialysis in this context) may provide a therapeutic opportunity for local drug delivery. Drug delivery by this technique will be limited by the local tortuosity properties of the tumor and potential toxicity from the extremely high concentrations of drug that can be obtained in the immediate vicinity of the probe.

Conclusion

Microdialysis is a powerful tool for studying brain neurochemistry in health and disease. The scientific basis is sound and technology is mature and accessible; therefore, more widespread use of this technique in clinical neuro-oncology can be anticipated. Use of well-established biomarkers such as glucose, lactate, glycerol, and glutamate may provide basic insights into brain tumor biology and response to therapy. Microdialysis also provides a method of biomarker discovery and pharmacokinetic analysis that can complement the extraordinary advances in contemporary oncogenomics and neuro-imaging. Finally, microdialysis probes can conceivably be used to deliver therapeutic agents while allowing simultaneous monitoring of biological effects of the therapy.

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