187 Microdialysis

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Background

The recent advent of in-vivo electrical and chemical monitoring in the human brain provides opportunities to study markers for individual disease processes and responses to therapy in functional disorders. Cerebral microdialysis is one such method for monitoring the local neurochemical environment of a target brain region of interest. The first description of cerebral microdialysis in the literature is by Bito et al. in 1966. He implanted a dialysis membrane filled with dextran solution into canine cortex and found that amino acid levels in brain extracellular fluid were greater than in cerebrospinal fluid [1]. Capitalizing on and refining this method, Ungerstedt et al. implanted a small loop of dialysis tubing in rat brain and continuously perfused it with a fluid medium. High performance liquid chromatography with electrochemical detection was used to identify and quantify amino acid concentrations in the dialysate [2]. Interestingly, when cerebral microdialysis was eventually translated to use in human patients, one of the first applications was in functional neurosurgery for Parkinson's disease patients undergoing thalamotomy [3]. Additionally, commercially available probes, dialysis fluids, collectors and analyzers have been created, improving access to the technique and making the use of this potentially complicated bedside monitoring more convenient and feasible. In essence, this methodology provides a window into the dynamic microenvironment of cortical and deep brain structures, as any extracellular molecule smaller than the dialysis membrane can be selectively sampled.

Principles of Microdialysis

Definition

Cerebral microdialysis is a tool to identify and measure concentrations of extracellular neurochemicals within cerebral structures, locally and in vivo. A double lumen probe containing an inlet and an outlet port (generally separate small tubes) are surrounded by a semi-permeable membrane which is sealed above and below a point at which the two tubes are inserted into the membrane lumen. This dialysis probe is then placed through a burr hole to a preset depth within the brain parenchyma. A perfusion solution with an electrochemical concentration similar to the local environment is propelled through the inlet tube and into the semi-permeable membrane (› *Table 187-1*). Molecules in the extracellular space, smaller than the permeable membrane, diffuse across it into the perfusion solution. The solution then flows through the outlet port and is collected in vials for further processing and analysis (› *Figures 187-1* and › *187-2*). The most frequently measured substances and their published reference values are listed in › *Table 187-2*. The novelty of microdialysis compared to prior open ended "push-pull" perfusion techniques is the addition of the semi-permeable membrane. This feature maintains the integrity of the adjacent interstitial tissue and prevents inaccuracy due to perturbation of the local environment from fluid leakage [7,18]. To date, cerebral microdialysis is the most commonly used technique for sampling neurochemicals in deep brain structures in vivo for both pre-clinical and clinical research purposes.

Table 187-1

Components of microdialysis perfusion solutions

Chemical	Artificial CSF (mM/L)[a]	Artificial CSF (mM/L)[b]	Ringer's solution (mM/L)[b]	Normal saline (mM/L)[c]
	Distilled water	Distilled water	Ringer's solution	Distilled water
NaCl	140	145	147	154
KCl	2	3	4	-
$CaCl_2$	1.2–2.4	1.4	2.3	-
$MgCl_2$	1	1	-	-
Na_2HPO_4	1.2	2	-	-
NaH_2PO_4	0.27	-	-	-
Glucose	7.2	-	-	-
	pH 7.4	pH 7.4	pH 6–6.3	

[a]Stamford et al., 1992
[b]Amara et al., 1998
[c]Bullock et al., 1995

Figure 187-1

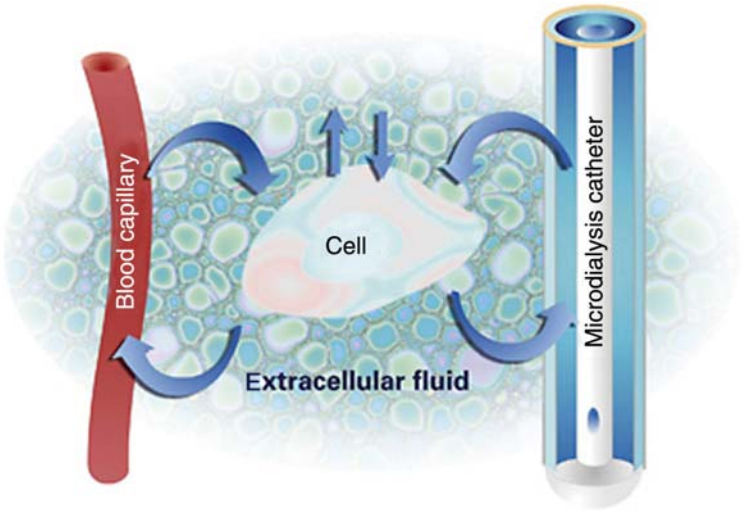
Techniques – Methods of Analysis

After collection, the dialysate vials may be stored at −20 to −70°C or immediately analyzed using a variety of techniques [4,19]. There are commercially available assays for the most common markers including glucose, lactate, pyruvate, and glycerol. Biogenic monoamine analysis requires more complex techniques and equipment. High performance liquid chromatography with electrochemical detection (HPLC EC) provides a high sensitivity and specificity method for measuring biogenic amines, in particular noradrenaline (NA), dopamine (DA), and serotonin (5-HT) [7,18,20]. For amino acids including glutamate, aspartate, GABA, serine, and taurine, HPLC with fluorometric analysis may be used according to published techniques [20].

Technical Considerations and Limitations

Microdialysis is a particularly attractive tool for in vivo monitoring of extracellular molecules in the brain because a substance of any type which

Figure 187-2



is smaller than the pore size of the semi-permeable membrane can be measured as long as some detection method is available. As with any technique, however, the unique limitations and issues which may influence either the use or interpretation of data generated from microdialysis must be carefully considered before proceeding with a particular application. First, the invasiveness of the technique presents risks for hemorrhage, neuronal damage, or infection, which is why this method has generally been applied in humans only when invasion of the brain is already being performed toward a therapeutic end. There have been few reports of significant complications from microdialysis in the literature, but there remains to be a systematic review of the overall safety profile of this still experimental technique. Therefore, patients and/or families must be made aware and consented for the possibility that microdialysis could slightly increase these risks beyond those already present for the therapeutic intervention.

The accuracy of microdialysis can also be affected by multiple factors. For example, the absolute concentration of a substance is difficult to determine because it is dependent on the flow rate. If the flow rate is too rapid, a steady state concentration of a chemical between the dialysate and extracellular fluid will not be achieved, leading to an underestimation of concentration. Some researchers have increased the probe length in order to improve this limitation; however, a larger probe size leads to more interstitial tissue damage and decreased spatial resolution [18,21]. This is of particular importance in functional neurosurgical applications as compared with trauma, since deep brain targets are often relatively small, so a longer length of dialysis membrane may not restrict sampling to only the desired target. A second factor affecting accuracy is the local tissue damage that occurs at the time of insertion. Studies have shown extremely high initial levels of monoamines immediately post-implantation, with subsequent normalization of values. These authors postulated that neurotransmitters may be released en masse from damaged cells and values do not accurately reflect the normal extracellular environment until they plateau at lower levels, reportedly between 2–24 h [4]. Third, a local fibrotic reaction has been shown to develop around the probe tip during chronic microdialysis experiments. This fibrosis correlates

Table 187-2

Published microdialysis markers in normal and diseased states

Marker	Normal value per liter	Observed trend	Disease state or process	Diagnosis	Location of probe	References
GABA	35–52 nM	↑	Seizure	Epilepsy, PD	Hippocampus	(4–6)
					Basal Ganglia	
Glutamate	240–480 nM	-	-	PD	Basal Ganglia	(4)
Glutamate	16 ± 16 μM	↑	Hypoxia/Ischemia, Excitiotoxicity, Neuronal death	TBI, SAH, Stroke, Tumor, Necrosis, Seizure	Cortex	(7–11)
	14 ± 3.3 μM					
DA	-	↑	Working memory, L-DOPA treatment	Epilepsy, PD	Amygdala Thalmamus	(3,12)
NO	-	↓	Vasospasm, Ischemia	SAH	Cortex	(13)
Glucose	1.7 ± 0.9 mM	↓	Hypoxia/Ischemia, Hypoglycemia, Cerebral hypermetabolism	TBI, SAH	Cortex	(7,9,10)
	2.12 ± 0.15mM					
Glycerol	82 ± 44 μM	↑	Hypoxia/Ischemia, Cell membrane breakdown	TBI, Seizure	Cortex	(5,7,9,10,14)
	81 ± 12.4 μM					
Lactate	29 ± 0.9 mM	↑	Hypoxia/Ischemia, Cellular redox states, Decreased glucose supply, Mitochondrial dysfunction	TBI, SAH, Epilsepsy, Intracranial hypertension	Cortex	(7,9,10,14–16)
	3.06 ± 0.32mM					
Pyruvate	166 ± 47 μM	-	-	-	-	(9,10)
	151 ± 12 μM					
L/P[a]	23 ± 4	↑	Hypoxia/Ischemia, Cellular redox states, Decreased glucose supply, Mitochondrial dysfunction	TBI, SAH, Epilsepsy, Intracranial hypertension	Cortex	(7,9,10,14–16)
	19.3 ± 1.7					
L/G	1.62 ± 0.18	↑	Cerebral hypermetabolism	Epilepsy	-	(9,17)

GABA: Gamma-aminobutyric acid; PD: Parkinson's Disease; TBI: Traumatic brain injury; SAH: Subarachnoid hemorrhage; DA: Dopamine; L-DOPA: Levodopa; NO: Nitric oxide; L/P: Lactate to pyruvate ratio; L/G: Lactate to glucose ratio

[a]most reliable marker of ischemia; – not available

with decreased basal concentrations of neurochemicals sampled after approximately 5–7 days, thus bringing the accuracy of values obtained after extended periods into question [18]. Finally, placement of the catheter may not be exact and should be confirmed if it is to be concluded that the data reflects the physiology of a particular target structure. Early methods of microdialysis

did not provide a method for confirming the accuracy of probe placement; however, recent studies and commercially available probes contain a radio opaque marker at the tip for confirmation of placement by CT scan or X-ray [4]. Again this is particularly important when microdialysis is used for functional neurosurgical procedures, such as Parkinson's disease and epilepsy, since conclusions based upon the data generated are only valid if the samples are obtained from the brain region being targeted.

While the local nature of the microdialysis is usually desirable to specifically analyze a target brain region, in other circumstances this can be a limitation. Unlike jugular venous oxygen sampling and positron emission tomography which are hemispheric or global investigative techniques, the information obtained from microdialysis represents the environment of approximately 1 cm around the probe tip. This information is usually not representative of the entire brain and must be used in conjunction with other monitoring modalities in order to safely direct patient care. This is more important when microdialysis data will be used to influence therapy, such as in trauma or ischemia situations, since focal data is used to direct global therapy. When microdialysis is used to better understand the physiology of a brain target in functional diseases, however, this focal measurement is far more desirable than a less relevant global or hemispheric analysis.

Finally, one must always remember what neuronal functions are in fact being measured by microdialysis. The neurochemicals sampled are a product not only of synaptic release, but also of local metabolism, capillary delivery and neuronal release and uptake from groups of cells [5,19]. The diameter of most microdialysis probes is fairly large from a cellular standpoint (usually several hundred microns), and this is difficult to overcome since the membrane diameter must be larger than the combined diameters of the inlet and outlet tubes which are inserted into the membrane. This is far too large for sampling synaptic activity in isolation (which would require a probe in the single digit micron range), so all microdialysis probes used to date measure tissue levels of neurochemicals rather than synaptic levels. This is important to understand when interpreting data, since a negative result with microdialysis does not necessarily mean that there is, in fact, no change in synaptic neurotransmitter levels. Conversely, the implications of positive results must be considered within the context of the limitations of the probe as a measure of local tissue rather than synaptic levels. Nonetheless, there are numerous applications of microdialysis which provide unprecedented opportunities to understand living human brain physiology even when these issues are taken into account, and several of these applications are reviewed below.

Uses in Human Patients

Despite its limitations, microdialysis has been successfully used as an adjunct to traditional research and therapy in many human patients. Recent years have seen an increase in the use of microdialysis as a clinical tool in a variety of neurosurgical disease processes, particularly traumatic brain injury and subarachnoid hemorrhage, where an opportunity exists to detect and prevent secondary cerebral injury [5,7]. Other neurological diseases with focal origins of pathology such as movement disorders and epilepsy have been studied using microdialysis as a research tool. Electrical recording in the human brain has provided a wealth of data regarding neuronal firing patterns in functional disorders, and functional imaging provides a non-invasive window into certain physiological changes in the living human brain. However, microdialysis is a minimally invasive method with a proven safety record to directly analyze nearly any substance within brain tissue with much higher resolution than functional imaging. This provides

unprecedented opportunities to sample local neurochemical environments of deep brain structures which can then be correlated with other data in order to better understand the physiological basis for human neurological disease. An overview of the most recent utilization of microdialysis reveals its widespread applicability.

Traumatic Brain Injury

Traumatic brain injury causes immediate cell death, in part from mechanical forces that result in diffuse axonal injury and vascular damage [8,22,23]. This primary injury also initiates a subsequent heterogeneous cascade, including disruption of ion channel pumps, leading to extreme shifts in intra and extracellular chemicals, massive increases in excitatory amino acids, and the generation of oxygen free radicals. The simultaneous activation of these pathways significantly increases cellular metabolic demands and ultimately result in neuronal injury and death [8].

While primary cell death after brain trauma may not be a reasonable target for intervention, secondary cerebral injury may benefit from early detection and neuroprotective strategies. Cerebral microdialysis is one tool that can provide early detection of factors leading to delayed neurologic insults. Changes in several neurochemical markers are indicative of neuronal risk (*Table 187-2*). For example, increased lactate, lactate to pyruvate ratio, lactate to glucose ratio, and hypoxanthine levels have been associated with increased metabolic demand or decreased nutrient supply in brain injured patients [24,25]. Furthermore, a corresponding decline in pH may warn of the shift from efficient aerobic to inefficient anaerobic metabolism [26]. These findings have been correlated with a decrease in local brain tissue oxygen partial pressures, ischemia, infarction and ultimately poor outcome [5,25,27–30]. As part of a multimodality monitoring system, microdialysis may detect these changes in advance of permanent cerebral injury, opening a treatment window to prevent these secondary insults and improve patient outcome.

Subarachnoid Hemorrhage

A similar paradigm exists for the detection, prevention and reversal of secondary cerebral insults for the treatment of subarachnoid hemorrhage. Vasospasm and its resultant cerebral ischemia is a major cause of morbidity and mortality after aneurysmal subarachnoid hemorrhage. Several studies have examined the patterns of neurochemical changes using cerebral microdialysis in this patient population in order to better understand the mechanisms of vasospasm and define markers of early detection. Increased levels of lactate, lactate to pyruvate ratio, glutamate and glycerol, as well as decreased glucose concentrations have all been observed in patients with clinical vasospasm [31]. Furthermore, microdialysis levels of nitric oxide, a proposed etiologic agent of vasospasm, have been shown to be significantly lower in patients during severe clinical vasospasm. These depressed levels also correlated with decreased brain tissue oxygen partial pressure values [13]. Most recently, cerebral microdialysis in conjunction with proteome-wide screening has been used to define two protein markers, heat-shock cognate 71kDa protein (HSP7C) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), as possible early markers of vasospasm. Levels in patients experiencing vasospasm were significantly different than in patients without vasospasm. Furthermore, this difference was detected approximately 4 days prior to the onset of clinical spasm [32].

Ischemic Stroke

Another avenue for clinical investigation using microdialysis has been ischemic stroke. Although

only a few studies have been conducted on this topic, they have focused on detecting elevations in excitatory amino acids. Bullock et al. demonstrated massively increased and sustained levels of both aspartate and glutamate in the infarcted tissue of a patient with a large hemispheric stroke. They postulated that the delayed release of excitatory amino acids may contribute to further infarction within the penumbra leading to malignant edema [33]. A subsequent study found that significant increases in microdialysis levels of glutamate and lactate to pyruvate ratio were associated with malignant edema, thus acting as potential indicators for decompressive hemicraniectomy [34]. Future investigations may consider focusing on the association between neuronal microdialysis markers after reperfusion using chemical thrombolytics or mechanical thrombectomy, although the safety of maintaining an implanted intraparenchymal probe during active systemic thrombolysis remains unclear and must seriously be considered before combining microdiaylsis with such therapies. Additionally, the relevance of any of these results to therapeutic outcome remains unclear in the absence of correlation with long-term outcome measures.

Epilepsy

An imbalance of neurochemical factors has long been proposed to underlie the onset of seizures and neuronal damage associated with epilepsy. A combination of excess production or decreased reuptake of excitatory neurotransmitters such as glutamate or conversely, decreased production or increased reuptake of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA) may contribute to seizure foci [35]. During and Spencer were the first authors to document the use of microdialysis to study human epilepsy patients, addressing the hypothesis that increases in extracellular glutamate may trigger spontaneous seizures [35]. In patients with complex partial epilepsy refractory to pharmacologic treatment undergoing planned depth electrode placement, they combined the depth electrode with a microdialysis probe. This combined probe was named a dialytrode [35]. The microdialysis probe was attached to a polyurethane/silastic flexible depth electrode with nichrome contacts. A sterilized, pyrogen-free, artificial extracellular fluid was perfused through the dialysis probe at a rate of 2.5 μL/min. Given the small dead space of the outlet tubing, a temporal delay of only ten minutes occurred between sampling and collection. After confirmation of placement of the combined electrodes by MRI, patients were transferred to the neurosurgical ICU where continuous video EEG monitoring and collection of dialysate every 30 min was performed using an automated sampler (CMA200, Carnegie Medicin, Stockholm, Sweden). Frequency of sampling was increased during a seizure. Analysis of amino acids in the dialysate was performed using HPLC (Bioanalytical Systems Inc., West Lafayette, In, USA) [35]. Of the six patients studied, results demonstrated that extracellular glutamate significantly increased prior to and during a seizure. Moreover, concentration of extracellular GABA increased during a seizure, most notably in the non-epileptogenic hippocampus.

In addition to this study, a similar experimental setup was used by these authors to evaluate the extracellular levels of lactate within the hippocampus of partial complex epilepsy patients undergoing bilateral depth electrode placement. An increase in lactate concentration of 91 ± 32% for 60–90 min following a seizure was observed. Of note, in patients without secondary generalization, this finding lateralized to the side of the seizure. Furthermore, interictal spikes were also associated with a significant increase in extracellular lactate levels. As a result of these findings, the authors postulated that seizures and interictal excitatory events increase the local, non-oxidative glucose metabolism of neurons. In addition, the increase

in local lactate levels directly decreases extracellular pH, a condition known to suppress seizures. This phenomenon may be responsible for the arrest of ongoing seizures and the postictal refractory period [15].

This group also utilized cerebral microdialysis to evaluate local, extracellular levels of antiepiletic drugs, namely phenytoin and carbamezapime. After systemic administration of these medications, simultaneous extracellular fluid (ECF) levels via cerebral microdialysis and unbound serum levels were obtained and analyzed. The ratio of ECF to serum concentrations were between 0.84 and 0.87 suggesting a significant correlation between local cerebral and systemic levels. Given the indirect mechanisms of newer antiepileptic drugs, the authors discuss the potential of cerebral microdialysis for studying their complex, local effects [36–38].

An extension of the combined microdialysis and depth electrode, containing single-unit recording microelectrodes, was created by Fried et al. By placing probes trans-occipitally into the hippocampus, amygdala, entorhinal cortex, posterior parahippocampal gyrus, orbitofrontal cortex, and cingulate cortex they gathered samples from 86 probes in 42 patients. Sampling occurred routinely at 30 min intervals, or 5 min intervals during events, over a 6 day period. The proposed temporal delay given the length of the outflow tubing was reported to be 20 min. Overall, the authors found an increase in the excitatory amino acids glutamate and aspartate as well as the inhibitory amino acids tuarine and GABA in the ipsilateral amygdala during seizure events [20].

Learning and Memory

Pilot studies conducted by Fried et al. in seizure patients with combined depth electrode, single-unit recording microelectrode and microdialysis probes noted changes in dopamine levels during cognitive tasks [20]. More recently, however, this group has used this technique to perform detailed experiments assessing the role of dopamine in specific learning and memory tasks. In ten patients with 16 probes placed in the central and basolateral nuclei of the amygdala, they analyzed samples of dialysate at 5 min intervals before, during and after either working memory, reading or word-paired associates learning tasks. As predicted, there was a significant increase in extracellular dopamine concentration throughout the presentation of various tasks. Interestingly, the magnitude of the change was dependent on task order, where the greatest increase above baseline was achieved when a memory task followed a reading task. The authors concluded that the human mesolibmic dopaminergic system has sustained activation during the performance of cognitive tasks. Moreover, as a higher level of dopamine was observed during working memory tasks when presented second, there is a relationship between amygdala dopamine release and novelty of stimulus [12]. This study highlights the potential power of microdialysis combined with other monitoring modalities and functional neurological assays to provide insights into human brain functioning which can be difficult to extrapolate from preclinical animal experiments.

Movement Disorders

Another field that has capitalized on the use of surgically placed deep brain probes to study the local neurochemical environment with microdialysis is functional neurosurgery for movement disorders, in particular Parkinson's disease (PD). Stefani et al. published studies describing intraoperative microdialysis during bilateral deep brain stimulation (DBS) in six patients undergoing surgery for refractory PD. In the acute period immediately before, during and one hour after placing DBS in the subthalamic nucleus (STN), they measured GABA, cyclic

guanosine 3′,5′-monophosphaste (cGMP) and glutamate. After the initiation of DBS, significant increases in cGMP of 200 and 481% above baseline were noted in the putamen and internal globus pallidus (GPi), respectively, while a decrease in GABA concentration of 25% below baseline was noted in the anteroventral thalamus (VA). Additionally, they found a significant increase in cGMP in the substantia nigra reticulata that coincided with increased neuronal firing during electrophysiological recordings. They postulated that these findings represent mechanisms that differentially affect fibers crossing the STN area. The STN-GPi pathway demonstrates activation while the GPi-VA pathway demonstrates inhibition, both contributing to a restoration of physiologic putamen activity [39–43].

Based upon the earlier epilepsy work described above, we developed an in vivo microdialysis method for continuous chronic sampling of local neurotransmitter concentrations in the subthalamic nucleus (STN) and substantia nigra reticulate (SNr) of patients for several days following implantation of STN deep brain stimulation (DBS) electrodes [4]. Six patients undergoing bilateral DBS for medically refractory Parkinson's Disease also received unilateral implantation of a microdialysis probe, inserted through a twist-drill hole adjacent to the burr hole for the permanent DBS electrode. In four patients, the probe was placed in the STN (1 mm away from the DBS electrode) and in two the probe was placed in the SNr at a depth of 3–4 mm ventral and 1 mm lateral to the DBS probe. Artificial CSF propelled by a portable CMA 107 pump (CMA Microdialysis, Stockholm, Sweden) was used to perfuse the membrane. Sampling occurred daily up to postoperative day 4 and during collection periods, samples were obtained at 3–10 min intervals. In two patients, the probe ceased to function on day 3. The samples were manually collected and analyzed using HPLC.

Several novel technical methods were used in this investigation due to the unique nature of the patient population under study. At the time, commercially-available microdialysis probes were not impregnated with any material which could be visualized radiographically (this has since changed), so published studies to that point in trauma and subarachnoid hemorrhage did not document the location of the probe. Given the large area influenced by those diseases, and the cortical position of the probes in most cases, this was not believed to be limiting. However, given the extremely small size of the STN and the SNr, and their deep locations, it would be difficult to draw conclusions regarding the physiology of these structures from the neurochemical data if there was no documentation that the probe was actually in the desired location. For the epilepsy studies, this was not an issue since the depth electrode fused to the microdialysis probe could be visualized. However, those electrodes were eventually removed prior to surgical resection, whereas the DBS electrode is a permanent implant. Therefore, it was not possible to fuse the microdialysis probe to the DBS electrode without either leaving the probe permanently in the brain or replacing the system after microdialysis with a new DBS electrode, both of which were unacceptable. Therefore, we chose to fuse a microelectrode wire to the microdialysis probe up to the beginning of the exposed membrane, but the membrane was not fused similar to what was done with the epilepsy dialytrode. With this, the probe could be visualized on intraoperative X-ray and on post-operative CT scans. This was critical, since a CT scan was performed on each patient following completion of the microdialysis sampling on day 3 or 4 after surgery, and the location relative to the DBS electrode confirmed that the probe location remained unchanged throughout the entire sampling period, so that all of the generated data reflected the neurochemical environment of the planned target in these patients. In addition, commercial probes at that time (and for the most part today as well) had a minimum exposed membrane length of

10 mm in the dorsal-ventral direction. While this is reasonable for large cortical areas subject to injury, for a structure such as the STN or SNr, this would be too long as this would sample not only the structure in question but several mm above and/or below that structure. Therefore, again based upon the prior epilepsy experience, we manufactured probes in the laboratory which had a diameter of just over 300 μm and a length of exposed membrane of only 3 mm. The inlet and outlet tubings had inner diameters of only 75 and 100 μm respectively, so that the deadspace was roughly 3 μl/m of tubing. Therefore, this probe not only sampled specifically and only within the target structures, but also had such a small deadspace that the lag time between sampling in the brain and collection at the end of the tubing was only a few minutes.

Overall, steady state levels of glutamate and GABA averaged 240 nM and 18–29 nM, respectively. GABA concentration was significantly higher in samples taken from the SNr compared to the STN; however, this difference was not appreciated for glutamate. A few conclusions were drawn from these studies regarding intrinsic steady state neurotransmission in these deep brain structures. The STN is mainly glutamatergic and the glutamate levels were on average 4–5 times higher than GABA levels in each patient. Conversely, the SNr is largely GABAergic and the levels of GABA in were 5- to 10-fold higher than in the STN. As a result, the authors concluded that the steady state neurotransmitter levels were largely a result of intrinsic neurons, as the less abundant neurotransmitter is released by synaptic inputs [4]. This also suggests the possibility that a neurochemical probe modeled on the microdialysis method could in the future be used either in addition to or in place of electrophysiological recordings for targeting these structures for DBS or other surgical interventions. Furthermore, although the relative difference in neurotransmitter between nuclei in this study was similar to results published during intraoperative sampling, the absolute amounts were different [40]. Though this could be explained by patient variability, it may also reflect treatment effect on local neurochemical environment as the former study's patients discontinued PD medications 2 weeks prior to surgery, while the latter discontinued medications on the day of surgery. Another possibility is the difference between acute and chronic sampling. In our study, the glutamate levels in the STN were substantially higher 2 h after surgery compared with 18–24 h later. Steady state was only reliably achieved by 36 h following surgery, at which point the daily levels were relatively consistent within patients. Therefore, it is possible that acute effects of insertional trauma may influence tissue neurotransmitter levels to a greater degree than previously appreciated. However, our study patients also had a DBS electrode inserted just prior to placement of the microdialysis probe, so the tissue trauma is likely to be far greater than when the microdialysis probe alone is inserted. Therefore, our early data immediately following surgery and for the ensuing 36 h may in fact be a neurochemical reflection of the microlesioning effect that is often seen for several days following DBS implantation. All six patients in this study had no complications at any point, and the microdialysis probes were completely removed without disrupting the DBS electrode location. Additionally, all patients had excellent clinical responses to their bilateral STN DBS. These findings highlight the potential for microdialysis to both define the normal physiologic environment within a deep brain nucleus and better elucidate the basis for pathologic disease states and mechanisms for treatment effects. It also suggests that such methods may be safely used to monitor brain neurochemistry even in situations where no brain tissue is to be removed or at risk and a device will be left permanently in place.

Less Common Uses

Although its implementation is not universal in neurosurgical centers, microdialysis use as a

research and clinical tool is becoming increasingly widespread, especially as commercially available setups such as CMA Microdialysis have received FDA approval. Other uses not mentioned in detail in this chapter include examining neurochemical marker profiles in patients with hepatic encephalopathy, hydrocephalus, malignant gliomas, and hyperventilation. Intraoperative studies have been conducted during lobectomy for TBI, aneurysm surgery, extracranial to intracranial carotid bypass, and spinal cord surgery in the dorsal root entry zone. Additionally, in the field of neuropharmacology, it is being used to measure extracellular concentrations of drug delivery to the brain and reverse microdialysis is being utilized for drug delivery [5]. Along with the more detailed studies outlined above, each of these applications reflects the versatility of microdialysis as both a research and clinical tool for analyzing human brain neurochemistry.

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