Clinical review

Science, medicine, and the future

Microdialysis

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Monitoring tissue chemistry in patients by microdialysis is likely to become routine in clinical practice

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Many diagnostic and therapeutic decisions in medical practice are based on measuring blood concentrations of endogenous molecules. Yet most biochemical and pharmacological events take place in the tissues. Assessing tissue chemistry should theoretically provide more accurate data, and this can now be achieved relatively cheaply and minimally invasively with microdialysis. This review describes the technique of microdialysis and its application in clinical research, drug monitoring, and drug development. It also discusses how, in the future, measurement of tissue rather than blood chemistry may become the standard for some clinical investigations.

Summary points

- Microdialysis enables the in vivo measurement of tissue chemistry in humans and is feasible in virtually every human organ
- It is currently being used to monitor brain ischaemia and metabolic control
- The technique is set to become a standard tool in drug monitoring and development
- In the future "bedside" microdialysis will allow monitoring of tissue metabolism in a wide range of diseases

Methods

This article is based on 10 years of personal experience of using microdialysis to monitor tissue chemistry in various clinical settings and on a comprehensive study of the literature. A Medline search at the time of writing provided 1020 articles for "microdialysis and human" and 7277 articles for "microdialysis."

Principles of microdialysis

In vivo microdialysis measures the chemical composition of the interstitial tissue fluid—that is, the fluid to which cells and other target structures are directly exposed. In contrast to imaging techniques or biosensors, which serve as detecting tools, microdialysis is a sampling tool and needs to be linked to an analytical device. Depending on the availability of an appropriate analytical assay, virtually every soluble molecule in the interstitial space fluid can be measured by microdialysis. In recent years the use of microdialysis has moved from preclinical evaluation and validation to clinical application, reflected by a considerable growth in the literature.[1–5] This development was catalysed by the increasing availability of extremely sensitive chemical detectors and detectors that require only a few microlitres of fluid.

The concept of microdialysis goes back to the early 1960s, when push-pull cannulas, dialysis sacs, and dialytrodes were inserted into animal tissues to study tissue biochemistry directly.[5] In 1974 Ungerstedt and Pycock reported on the use of "hollow fibers." These fibres were steadily improved and eventually resulted in the needle probe (fig 1) which is inserted by means of a guide cannula into the tissue. Today, several companies offer commercial microdialysis kits, and there are probes available that are EU approved for studies in human soft tissues and human brain. The cost of a disposable kit is roughly €250 (£150, $220).

Microdialysis is based on sampling of soluble molecules from the interstitial space fluid by means of a semipermeable membrane at the tip of a probe (fig 2).

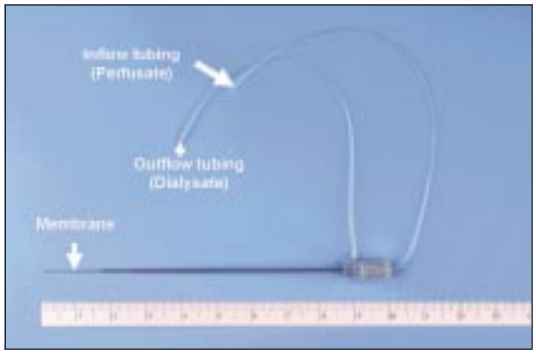

Fig 1 Needle type microdialysis probe with a semipermeable membrane at the tip. The probe can be inserted into tissue by means of a guide cannula. The probe's inflow tubing is connected to a microperfusion pump, and the probe is constantly perfused with a physiological solution at a rate of ~1 µl/min. Samples are continuously collected from the outflow tubing

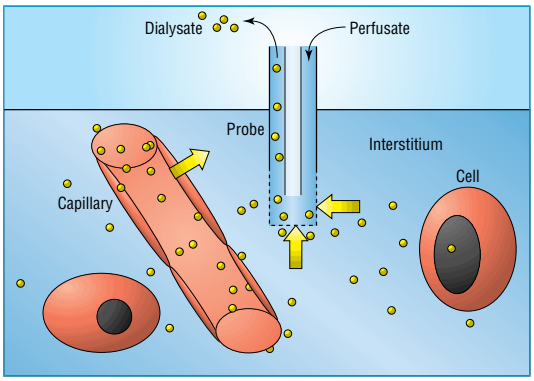

Fig 2 Diagram of a microdialysis probe. The semipermeable membrane at the probe tip allows exchange of soluble molecules between the probe and the surrounding tissue. When the probe is implanted into tissue interstitium, molecules continuously diffuse out of the interstitial space fluid into the perfusion medium. Samples are continuously collected and analysed by standard chemical analytical techniques

The probe is constantly perfused with a physiological solution, and when the probe is implanted into tissue molecules present in the interstitium diffuse across the membrane into the perfusion medium of the probe. Samples are either analysed on line or collected for later analysis. For most analytes the equilibrium between interstitium and the perfusion medium is incomplete, which is why microdialysis probes need to be calibrated.[6] Most calibration methods are based on adding the respective analyte to the perfusion medium and measuring its rate of disappearance through the membrane, which is taken as a measure of equilibration between the probe and the tissue. With proper calibration, intraindividual coefficients of variation for microdialysis measurements range around 20% depending on the analyte. Although microdialysis offers many advantages over other techniques, notably its potential to be performed in any clinical centre, it is currently limited by the availability of sufficiently sensitive chemical assays. Microdialysis with conventional dialysis membranes is also limited to dialysable molecules with a molecular weight of no more than about 50 kD, although the use of ultrafiltration membranes and metal meshes could raise this limit.

Initially microdialysis was designed to measure concentrations of neurotransmitters in rat brain, and was gradually adopted in other research.[5] The first published application of microdialysis in humans was a study on interstitial glucose in 1987,[6] and its use was initially confined to adipose tissue.[6 7] However, numerous reports have since appeared on microdialysis in other human tissues such as brain,[8] heart,[9] lung,[10] and solid tumours.[11]

From a practical point of view no special skills are required to insert a microdialysis probe. In soft tissues and the skin, the procedure can be managed by any health professional and is no more painful than the placement of an intravenous catheter. After about 10 minutes, most subjects do not report any pain at all. The probes are usually left in situ for several hours, but they can be left in place for up to several weeks. Studies of people during exercise are possible with flexible probes.

Application of microdialysis in clinical research

Monitoring ischaemia

Currently, microdialysis is most widely used in neurointensive care for monitoring secondary ischaemia, a common complication after brain trauma or intracranial haemorrhage that may seriously affect outcome.[12] Microdialysis reveals characteristic changes in the concentrations of energy related metabolites that may serve as earlier and more accurate markers of ischaemic events than brain pressure. Experiments show that an increase in glycerol concentration indicates damage of neuronal membranes and that an increase in the lactate:pyruvate ratio may be an early indicator of brain ischaemia.[13] Other studies indicate that reductions in cerebral blood flow are followed by a massive release of potentially neurotoxic excitatory amino acids.[14]

The potential of microdialysis to closely monitor patients with brain trauma led to its routine use as a clinical tool in Sweden, notably in Lund and Stockholm in the mid-1990s. Microdialysis monitoring has become part of the "Lund concept" for treating traumatic brain injury, which has dramatically reduced mortality in patients with severe head injuries.[15] This concept is based on physiological principles of volume regulation in the brain and on surgical and pharmacological interventions aimed at keeping capillary hydrostatic pressure and brain pressure low. The experience gained in Sweden provides evidence that microdialysis yields sensitive and early markers for secondary brain injury and helps to indicate whether therapeutic interventions are effective.[15] On the basis of these encouraging results, many academic centres for neurosurgery worldwide are about to implement microdialysis in routine care. Thus microdialysis will probably become fully integrated in routine monitoring procedures in intensive care.

Microdialysis has also been used to monitor concentrations of cardiac troponin T and aspartate transaminase for up to 100 hours after patients have undergone heart surgery.[9] Increased myocardial concentrations of these markers correlate with electrocardiographic changes and precede peak levels in serum by an hour. Gut ischaemia is another serious and difficult to

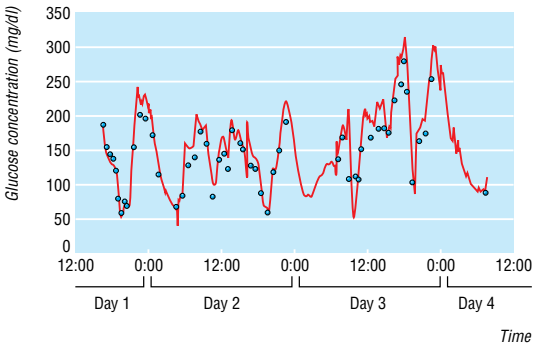

Fig 3 Continuous glucose recording in a patient with type 1 diabetes by means of microdialysis (black line). Capillary blood glucose concentrations (open triangles) were used for comparison. (Reproduced from Jungheim et al[18] with permission of the American Diabetes Association)

diagnose complication, at least in preclinical settings, that can be monitored by microdialysis.[16] For plastic surgery, microdialysis monitoring has been shown to be useful for indicating imminent ischaemia in myocutaneous flaps used in reconstructions.[17]

Monitoring glucose

Since publication of the diabetes control and complications trial (DCCT) the importance of long term metabolic control in patients with diabetes has been well recognised. Several devices have been developed for closely monitoring tissue glucose, including a portable microdialysis system that allows continuous measurement of subcutaneous glucose concentrations for up to several days.[7] Such devices offer the benefit of glucose analysis without the need for repeated invasive measurements and may be used to improve glycaemic control (fig 3). Ambulatory glucose monitoring with microdialysis is particularly suitable for patients with labile glycaemic control.[7] Although the lack of suitable automated online glucose analysers hampers its routine application, microdialysis can be used in selected patients to improve metabolic control.

The role of microdialysis in clinical pharmacology

Antibiotic drug research

Because microdialysis measures concentrations of unbound (that is, pharmacologically active) drugs in the interstitium (the target site for many bacterial infections) the technique has led to a reappraisal of concepts of "tissue-penetration" by antimicrobial drugs.[25 26] Microdialysis data indicate that in healthy people interstitial concentrations of β-lactams are in the range of free serum concentrations, whereas interstitial levels of chinolones and macrolides are considerably lower than those predicted from biopsies. For several conditions, notably septicaemia and septic shock, tissue concentrations of antibiotics such as piperacillin may be subinhibitory even though effective concentrations are attained in serum.[26 27] This may explain therapeutic failures and the emergence of drug resistant bacteria that were exposed to subinhibitory drug concentrations in tissue.

Current clinical research applications of microdialysis

- Elucidating the chemical basis for initiation of seizures (such as pre-epileptic increase in glutamate and a consecutive surge in γ-aminobutyric acid[8])
- Studying neurochemical patterns in defined brain areas (such as increased dopamine release in human amygdala during performance of cognitive tasks[19])
- Studying local physiology of adipose tissue, muscle, and skin[20–24]
- Measuring peptides and metabolites at site of action or release and describing paracrine regulations in select organs or tissues such as the ovary and subcutaneous fat[20]
- Administering drug locally by microdialysis without inducing systemic side effects and simultaneously measuring the corresponding tissue response, such as catecholamine induced lipolysis[20]

Anticancer agents

Microdialysis studies of tumours are of considerable interest with the recognition that insufficient drug penetration into the interstitium of solid tumours represents a rate limiting step in clinical response to chemotherapy.[28] Microdialysis studies in patients with breast cancer and melanoma revealed no association between serum concentrations of anticancer drugs and tumour exposure to the drugs.[11 25] However, there is preliminary evidence that the concentrations of cytotoxic drugs in a tumour may correlate with response to chemotherapy.[11] These findings cast doubt on the use of serum drug concentrations to predict response and corroborate previous findings of a high variability of drug penetration into tumours. Microdialysis may therefore prove to be a good method for selecting compounds with favourable penetration characteristics and may help to identify patients who are unlikely to benefit from chemotherapy because of poor drug penetration.

Topical drugs

Topical application of drugs is an attractive way to circumvent systemic side effects, but it is often not clear whether adequate drug concentrations are reached in the tissue. Microdialysis permits this issue to be addressed and could be used to identify formulations and doses of topically applied non-steroidal anti-inflammatory drugs that produce effective local concentrations.[29] The use of microdialysis in topical drug research may thus lead to a critical reappraisal of cost benefit ratios of topically administered drugs.

Drugs in the central nervous system

Microdialysis has been used to measure several drug concentrations directly in human brain parenchyma[25] and may help to define optimal drug penetration across the blood-brain barrier for patients such as those infected with HIV. The success of preclinical microdialysis indicates ample opportunity for clinical neuropharmacological studies. In contrast to preclinical studies, however, there are serious ethical limitations for human drug studies, mainly the small

Additional educational resources

Reviews

- Lönnroth P. Microdialysis—a new and promising method in clinical medicine. *J Intern Med* 1991;230:363-4
- Ungerstedt U. Microdialysis—principles and applications for studies in animals and man. *J Intern Med* 1991;230:365-73
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Useful websites

American Association of Pharmaceutical Scientists (AAPS), Microdialysis Focus Group (www.aapspharmaceutica.com/resources/focus/microdial.html)

CMA/Microdialysis (www.microdialysis.se)
A useful and frequently updated commercial website about basic methods and latest developments in microdialysis research

Cutaneous Microdialysis Club (www.physiologie1.uni-erlangen.de)

number of clinical settings where such studies would be ethically appropriate.

Future developments

Given the recent developments in microdialysis techniques, it seems likely that microdialysis will become available for a broad range of diagnostic applications. Besides its role as a research tool, it will become an integral part of neurointensive care monitoring and standard for measuring drug distribution in drug development. Miniaturisation and online automisation of chemical assays will ultimately allow "bedside microdialysis" for assessing antibiotic penetration of infected organs and monitoring tissue metabolism in disease states.

Competing interests: None declared.

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Lesson of the week

Immobilisation of the cervical spine in children

Sophie Skellett, Shane M Tibby, Andrew Durward, Ian A Murdoch

Recognition and early management of children at risk of injury to the cervical spinal cord is lacking

continued over

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Trauma to the cervical spine accounts for 1.5% of admissions in children with trauma in the United States, 35% of which have an associated injury of the cervical spinal cord.[1] Such an injury may occur along with bony or ligamentous damage. Ligamentous damage encompasses injury to the spinal cord without radiological evidence of abnormalities.[2] Immobilisation of the cervical spine is mandatory in patients at risk to prevent the development of injury to the cervical spinal cord and its progression.[2–4]

Most children requiring hospital admission for trauma are considered at risk of injury of the cervical spinal cord. The commonest causes are road crashes, falls from greater than 4.6 metres, head injuries, and injuries elsewhere to the spine.[5 6] These patients require immobilisation of the spine, commonly achieved with a rigid collar and a supplemental device. Immobilisation should be discontinued only after exclusion of bony and ligamentous damage, which needs an adequate clinical examination.[7] Important features of the examination are neck pain, midline tenderness on palpation of the neck, and any signs or symptoms of neurological injury.[8] This is possible only in a conscious patient (Glasgow coma score >13) who does not have painful distracting injuries. The negative predictive value of clinical examination is almost 100%.[8] Radiological evaluation plays a part, initially in identifying unstable fractures requiring urgent surgery.

As the lead centre for paediatric intensive care in the south east of England, Guy's Hospital provides a retrieval service for three paediatric intensive care units, collecting patients from over 30 district general