Probe Scientific Ltd

Microdialysis and Continuous Automated Real-Time Online Monitoring using Biosensors

Dr Mark T. O’Connell
Director
Microdialysis

A technique used to determine the chemical components of the fluid in the extracellular space of tissues ‘mimics small blood vessels in tissue to enable dynamic monitoring of biochemical or pharmacological processes within a living body’
Micro dialysis

A process in which particles of different kinds are selectively removed from a liquid as a consequence of differences in their capacity to pass through a membrane into another liquid.

Osmosis = The tendency of fluids separated by porous septa to pass through these and mix with each other; the action of this passage and intermixture.
"The capability and reliability of the microdialysis technique for measuring endogenous substances as well as exogenous therapeutic agents in various tissue systems have brought it to the forefront of the in vivo tissue sampling methods”

Chandra Chaurasia, FDA

*Biomed Chromatogra* 1999, 13: 317-332
Microdialysis principle
Microdialysis principle
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Specifications

- Hollow fibres
  - 0.22 – 1+ mm Ø
  - > 10 µm wall thickness
  - MWCO ~2 – 3,000 KDa
  - Material e.g. polyethersulfone

Bottom image: Scanning electron micrographs of the polyethersulfone (100 kDa MWCO) outer membrane surface
A microdialysis study of the in vivo release of 5-HT in the median raphe nucleus of the rat
A Adell & F Artigas,
British Journal of Pharmacology (1998) 125, 1361 ± 1367

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Figure 1 Effect of the perfusion of 1 μM tetrodotoxin on the output of 5-HT. Each point is the mean ± s.e.mean of five rats. See text for statistical details.

FIG. 5. KCl stimulation of cerebellar GABA release is not modified by IGF-I. No difference in the response of GABA to 100 mM KCl was seen when given in combination with 100 nM IGF-I. Similarly, the response of GABA to subsequent challenges of 100 mM KCl was not modified by previous exposure to IGF-I. Results shown are of a representative experiment. The pattern of GABA release was identical when 100 mM KCl was given alone (data not shown). This experiment was repeated with another animal, with identical results. The time corresponding to each sample is 10 min (tick marks on X-axis). Pulses of each test substance were applied for a time corresponding to four samples (40 min, asterisks).

Castro-Alamancos and Torres-Aleman
Multidisciplinary strategy within the same brain region

**b** Neuropharmacology
- Altered perfusion media
- Selective drugs

**Microdialysis**

**a** Neurochemistry
- On-line analysis

**c** Electrophysiology
- Recording electrode

Sampling site

Microdialysis probe with internal chlorided silver electrode
Microdialysis and on-line enzyme-amperometric analysis
Impairment of function ('penumbra')

Structural lesion

Minutes

Hours

Time

Days and weeks
Window of opportunity

Brain O₂

kPa

Hours
Graph showing brain oxygen ($P_BO_2$) and microdialysis concentrations of glutamate and lactate/pyruvate ratio during clipping of a complex recurrent giant ICA aneurysm that had rebled. Extended periods of temporary clipping (blocks) caused a sustained fall in $P_BO_2$ below 1.1 kPa for 40 minutes, with large increases in glutamate and L/P.
PERSONALISED MEDICINE...

- Understand degree of injury or disease
- Understand the time course of injury / disease progression
- Predict secondary events that contribute to outcome
- Target therapeutic approach
- Assess therapeutic success using surrogate end-point markers
Current practices for monitoring?
Blood Drug Concentration v Time
Conventional blood withdrawal
Blood Drug Concentration v Time using intravenous microdialysis
Offline application
Continuous automated online application

- **Peristaltic pump**
- **Biosensor flow cell and sensor**
- **Potentiostat**
- **Laptop running potentiostat software**
- **MicroEye®**

**OR**
- **Waste**
MicroEye®
Intravenous Microdialysis CGM (in vitro)

Valgimigli et al., ATTD2011 poster
MicroEye® Intravenous Microdialysis
CGM (in vitro)

Valgimigli et al., ATTD2011 poster
Third party run Clinical Trial. Results presented at the annual American Diabetes Association (ADA) Conference, June 2010

Accuracy of a novel continuous glucose monitoring system (CGMS) using intravenous (iv) microdialysis

Eric Zijlstra¹, Michael Hartlep², Mark O´Connell³,
Tim Heise¹, Wolfgang Künnecke²

¹Profil Institute, Neuss, Germany
²Trace Analytics, Braunschweig, Germany
³Probe Scientific, Coventry, United Kingdom
Online Continuous Glucose Monitoring

- **Physiological solution**
- **Micropump**
  - High perfusion 125 μL/min
- **Data recording unit**
  - 1-2 minute
- **Glucose sensor**
  - Electro-chemical (glucose oxidase)
- **Perfusion**
- **iv microdialysis**
Individual Glucose-Time Profile

Glucose Concentration (mg/dL)

Time (hh:mm)

OGTT (75 g glucose)
Individual Glucose-Time Profile

![Graph showing glucose concentration over time.](image)
Accuracy

- N = 1781 paired values
- Numerical point accuracy
- Mean absolute deviation 8.5 ± 8.2 mg/dL
- Mean relative absolute deviation 8.5 ± 7.7%
- Accurate readings (ISO-criteria) 89.7%
Accuracy

- Clinical point accuracy
- 99.3% Accurate or acceptable
- Zone A: 94.0%
  Zone B: 5.3%
  Zone C: 0.0%
  Zone D: 0.7%
  Zone E: 0.0%
Conclusions

- Novel CGMS using intravenous microdialysis
- No blood loss
- No physiological lag-time
- High perfusion rate and online CGM limiting technical lag-time
- No need for frequent calibration
- Good agreement with reference blood glucose concentrations
Continuous automated online application

- Peristaltic pump
- Biosensor flow cell and sensor
- Potentiostat
- Laptop running potentiostat software
Relative Recovery

Flow rate

Longer fibre

Shorter fibre

% 100

Flow rate 5 μl/min
Results
Ionic Reference Technique

Without IRT

With IRT

\[ r = 0.95 \]
\[ r = 0.97 \]
Microdialysis and Continuous Automated Real-Time Online Monitoring using Biosensors

- The microdialysis device provides an effective interface
- Continuous sampling provides a stream of analyte
- The online sensor provides trend data NOT discrete snapshots that must be modelled to provide pseudo-trends
- Real-data in real time so personalise medicine can be applied
- Windows of opportunity to prevent disease progression
- Better therapeutic approaches and the potential to use surrogate end-point markers to determine best practice