Use of Microdialysis to study Metabolism in Humans

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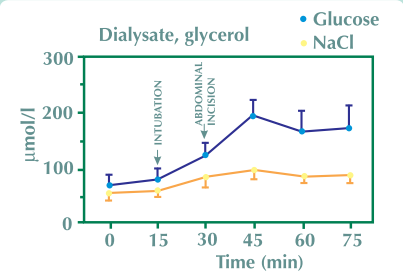
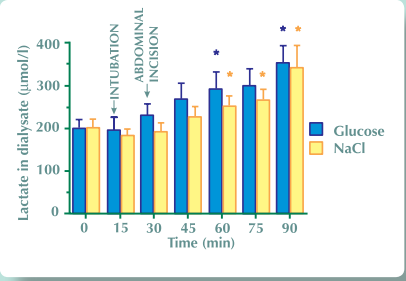
Question

Lipid and carbohydrate metabolism are affected by surgical intervention. Can microdialysis be used to continuously follow metabolism during surgery?

Method

Microdialysis in subcutaneous fat was carried out during open cholecystectomy. A 60 Microdialysis Catheter was used with a 106 Microdialysis Pump. The samples were analysed immediately in a 600 Microdialysis Analyser. Half of the patients received an intravenous glucose infusion and the other half saline during the operation. Lactate and glycerol were measured in the microdialysate.





Result

Levels of glycerol and lactate in the dialysate began to rise during intubation of the patients. This increase accelerated following the abdominal incision. The changes were more pronounced when glucose rather than saline was used for the infusion.

Conclusion

The results suggest that microdialysis can beused to continuously follow tissue metabolism in conjunction with abdominal surgery. Lactate and glycerol production in fat increases during the surgical intervention. The increases start during intubation and are accelerated by surgical intervention.

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References: G Felländer et al: 1) J ClinEndocrinol Metab 78:150-155, 19942) Nutrition 12:589-594

Principles of Microdialysis

Microdialysis is a way to examine the interstitial space of intact tissue. The microdialysis unit is a semipermeable membrane which is perfused with a neutral solution using a high performance pump. The microdialysis catheter is placed in the interstitial space of the tissue to be examined. Small molecules can pass in and out of the membrane during perfusion. The ingoing and outgoing microdialysate can be compared. The net changes reflect what is happening in the interstitial space. Microdialysis catheters, designed for use in man, are available from M Dialysis. The catheters can easily be inserted in human fat and muscle tissues and the metabolism in these tissues can be investigated. I have used these catheters for a long time and my experience is given below.

Studies of metabolite levels in peripheral tissues

Microdialysis can be used to continuously monitor changes in the concentration of various metabolises in adipose tissue and muscle. In particular glucose, lactate and pyruvate (reflecting carbohydrate metabolism) and glycerol (reflecting lipid breakdown through lipolysis) have been investigated.
It is also possible to study other small molecules which easily move through the membrane such as adenosine, urea and amino acids.
It is possible to determine the true interstitial concentration of various metabolises with microdialysis. One way is to perfuse the tissue at a high speed (1 -5 ml/min) with increasing concentrations of the metabolite to be determined. The differences in the concentrations of the metabolite inthe ingoing dialysis solvent versus the outgoing dialysis solvent are determined. From these differences the

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true concentration of the metabolite in the tissue can be calculated by a simple formula. Another way is to perfuse the tissue at avery low speed (0.3 ml/min) with a long dialysis membrane (30 mm). Then, the recovery (i.e.uptake of molecules from the interstitial space) is 100%, thus giving the true tissue concentration directly. M Dialysis has pumps and microdialysis catheters which allow such direct measurements. The "direct" technique is less time consuming than the indirect "calibration" technique. On the other hand, a rather long collection time is needed for the "direct" technique. It is therefore not suitable to use for short-term experiments when one, for example, wants to study the tissue every 5 min. Using either technique it has been possible to determine the true muscle and adipose tissue level of most of the metabolites mentioned above. Some new exciting findings have been obtained from various laboratories. First, it has been clearly demonstrated that lactate (originally thought predominantly to be produced by muscle) is produced insignificant amounts by adipose tissue. Second, it has been shown that glycerol (mainly thought to be solely produced by adipose tissue lipolysis) also is produced in large amounts in the muscle tissue by local lipolysis.

"...glycerol is also produced in large amounts in the muscle tissue by local lipolysis."

Determination of the tissue flow

Changes in the concentration of a metabolite in the interstitial space is determined by three major factors. Those are local production, local uptake or breakdown by the cells and removal by the tissue flow. In metabolic experiments it is therefore essential to get information about tissue flow. A technique has been worked out to indirectly measure the tissue flow with microdialysis.The flow marker is added to the ingoing microdialysis solvent. This marker is usually ethanol. The ratio of outgoing versus ingoing ethanol is determined. This ratio decreases when more ethanol is removed from the microdialysis device by the tissue indicating an increase in blood flow. An increase in the ratio means that less ethanol is removed from the microdialysis system reflecting a decrease in the tissue flow. The ethanol technique is so far only semiquantitative, i.e., it can be used to determine if blood flow increases or decreases but not at which rates these changes are occurring. However, various mathematical models are under development which might in the future be used to determine the true rate of tissue flow with the ethanol technique. When the ethanol technique is combined with measurements of metabolites (which can be made simultaneously in the same microdialysis probe) it is possible to get a rather good idea about changes in the production or uptake of a certain metaboliteby the tissue. Using the ethanol technique the effects of cathecolamines and insulin on interstitial flow in muscle and fat has been investigated in some detail.

"...lactate is produced in significant amounts by adipose tissue.

Regulation of metabolism

Metabolically active agents can be added to the ingoing microdialysate. During microdialysis the drugs leave the probe and act on the surroundig tissue influencing the tissue flow and the production and/or uptake of metabolites by the cells in the tissue. These metabolise changes in the tissue will be reflected by corresponding changes of the concentration of metabolites in the outgoing microdialysate. It is also possible to determine the metabolically active agent in the ingoing versus out-going dialysate and thereby get an idea about the concentration of this agentin the tissue surrounding the probe. Since microdialysis only takes place in a very small part of the total tissue it is possible to add a drug at a very high concentration (i.e., millimolar) to the microdialysis solvent causing a high local concentration of the drug, without getting any generalised effect of it on the organism. With microdialysis it has been possible to perform detailed pharmacological investigations of the adrenergic and insulin systems in human adipose tissue and skeletal muscle. Using this "pharmacological" approach the adrenergic receptors involved in the regulation of lipolysis and lactate metabolism as well as the mechanisms for how insulin acts on lipolysis and on carbohydrate metabolism and interstitial flow have been explored in some detail in human adipose tissue and muscle.

Summary

Microdialysis is available for clinical and experimental in vivo studies of the metabolism at the cellular level in man; metabolites with a small molecular weight can be investigated easily. M Dialysis has microdialysis catheter, pumps and analytical chemistry instruments which are designed for human studies. A number of different metabolites can be simultaneously measured using the same microdialysis catheter.The metabolite levels can be continuously monitored by microdialysis in skeletal muscle and adipose tissue; these tissues are easily available for human studies. By combining measurements of metabolites with measurements of the escape of ethanol from themicrodialysis system it is possible to get anidea about local production and uptake of metabolises in the tissue, since ethanol is atissue flow marker. Microdialysis can also beused in pharmacological experiments. It ispossible to add metabolically active agents atvery high concentrations locally to the tissue through the microdialysis system and then investigate the changes in tissue metabolite levels (and in tissue flow) which are induced by these agents. The microdialysis technique is easy to handle and safe for the subjects. It can be used to study children, elderly and critically ill patients without causing important discomfort.

References:1. Amer P. and Bülow J. Assessment ofadipose tissue metabolism in man:Comparison of Fick and microdialysistechniques. Clinical Science 85:247-256,1993.2.Lafontan M. and Arner P. Application of insitu microdialysis to measure metabolic andvascular responses in adipose tissue. Trends in Pharmacological Science.17:309313, 1996

application note 6