Commentary

How Minimally Invasive is Microdialysis Sampling? A Cautionary Note for Cytokine Collection in Human Skin and other Clinical Studies

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Abstract. It is common to refer to microdialysis as a minimally invasive procedure, likening it to insertion of an artificial capillary. While a comparison of this type allows the process to be easily visualized by those outside the field, it tends to provide a false impression of the localized perturbation of the tissue space that is caused by catheter insertion. With the increased acceptance of microdialysis sampling as a viable *in vivo* sampling method, many researchers have begun to use the technique to explore inflammatory and immune-mediated diseases in the skin and other organs. Unfortunately, many of the molecules of interest, particularly chemokines and cytokines, are known to be generated during the inflammatory response to wounding and the subsequent cellular events leading to wound repair. With more than 11,000 reports citing the use of microdialysis sampling, only a few researchers have sought to assess the tissue damage that is incurred by probe insertion. For this reason, caution is warranted when collecting these molecules and inferring a role for them in clinical disease states. This commentary seeks to remind the research community of the confounding effects that signaling molecules related to the wounding response will have on clinical studies. Proper controls must be incorporated into all studies in order to assess whether or not particular molecules are truly related to the disease state under investigation or have been generated as part of the tissue response to the wound incurred by microdialysis catheter implantation.

KEY WORDS: biocompatibility; cytokines; microdialysis; wound healing and repair.

INTRODUCTION

Microdialysis sampling is a well-established and widely accepted method for the *in vivo* collection of solutes from a number of complex matrices, but principally from the extracellular fluid space of animals including rodents and humans (1). The sampling method involves implantation of a small porous hollow fiber dialysis membrane into the tissue using a guide needle, which is subsequently removed, leaving the membrane in contact with the surrounding fluid-filled tissue space. Perfusion of the fiber allows the exchange of fluid and dissolved solutes between the outside tissue space and the perfusion fluid across the membrane, primarily by diffusion. This provides an analytically clean sample that

requires little to no further treatment before analysis. For this reason, microdialysis sampling has become a standard technique in many laboratories to examine the uptake and distribution of xenobiotics or explore the mediator mechanisms of physiological and pathological tissue events.

Microdialysis sampling techniques were first applied to studies in neuroscience, driven by the desire to quantify chemicals related to neurotransmission (e.g., dopamine and serotonin) and energy utilization (e.g., glucose and lactate) in the brain. The primary advantage with this technique in neuroscience is its ability to perform collections following pharmacological or physiological stimuli in conscious and freely moving animals. The successful application of this sampling technique by neuroscientists led to the development of microdialysis for the collection of xenobiotic compounds from many different tissue spaces in order to conduct pharmacokinetic and drug distribution studies. Most of the analytes recovered by microdialysis in these studies were of low molecular mass. More recently, there has been an interest in using microdialysis to recover macromolecules, particularly neuropeptides and cytokines, in order to explore the humoral regulation of disease-related inflammatory and immune cascades (2–5).

While microdialysis sampling is frequently referred to as a minimally invasive procedure and even sometimes referred to as a passive artificial capillary, it is clear that there are both acute and chronic tissue responses to the insertion of the probe, its subsequent perfusion and the process of dialysis.

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While there is a general awareness that a recovery and equilibration period following the insertion trauma needs to be incorporated into dialysis protocols, few studies have been performed that give guidance regarding the appropriate equilibration times after implantation. This article seeks to encourage those using microdialysis sampling for clinical studies, particularly for collection of chemokines, cytokines, and growth factors, to carefully consider how the wounding response evoked by the insertion of a microdialysis catheter may influence their study outcome. Additionally, as the interrelationship between that response and the analytes of interest may affect their results, the scientific interpretation of these results must also be carefully considered.

MICRODIALYSIS PROBE INSERTION AND TISSUE INJURY

Implantation of microdialysis probes into the majority of tissues involves either using a guide needle or removal of enough tissue fascia to allow probe insertion. It is known that this initial trauma causes some cellular damage and results in the perturbation of local blood flow (6) and localized bleeding due to physical damage to blood vessels (7,8). Studies in the brain provide a body of evidence showing that the implantation of microdialysis probes triggers a generalized injury response including edema (9–13). The damage occurs because microdialysis probes are generally much larger ($\geq 200\ \mu\text{m}$) than the surrounding tissue elements and adjacent blood vessels since the distance between blood vessels is usually less than $50\ \mu\text{m}$ (14). Disruption of the vascular architecture may thus be associated with an ischemic and/or hyperemic event and disruption of the blood tissue barrier (7,8).

There are very few reports about the time necessary for recovery from trauma associated with probe insertion or about the specific endogenous compounds generated as a result of this trauma. In many human studies, local anesthetics are used to minimize the pain of probe insertion. Consequently, the methods sections of papers describing dermal microdialysis usually state that a 2-h recovery period was allowed either for the local blood flow to return to normal (indicating the resolution of the immediate erythematous response to trauma) or a normal flare response to histamine to be re-established (indicating the recovery from the local anesthetic) (15). However, in the latter case, while high histamine levels, approximately $350\ \text{ng/ml}$, were observed immediately after implanting microdialysis probes in rat skin, they fell to less than $25\ \text{ng/ml}$ within 20 min (6), indicative of a much more rapid recovery from the initial histamine-mediated trauma response.

While the above may give an indication of the time necessary for the apparent “recovery and equilibration” of a tissue following the trauma of probe insertion, it is clearly not the end of the story as the more chronic cytokine-driven stages of inflammation are just beginning. For example, in Clough *et al.*, levels of IL-6 and IL-8 were low or undetectable within 1 h of probe insertion but rose significantly over the following 6 h (16). This observation that trauma stimulated the generation of IL-6 and IL-8 (CXCL8) extends previous microdialysis and skin blister studies, respectively (17–19), and is evidence of the sustained impact of probe

insertion to generate an early cascade of multiple cytokines. An approximate temporal sequence for the cytokine and growth factor response after a wounding event is shown in Fig. 1. Many of these factors have been shown to be present 24–48 h after probe insertion or possibly even longer (19). It is for this reason that appropriate controls be included in the experimental design to accommodate the very different time courses of cytokine generation (16,20).

It is critical to recognize that insertion of a microdialysis probe initiates an immune response which is similar to the response to any foreign object (21). The chemical signaling processes, involving both acute phase inflammatory mediators and cytokines, surrounding the probe means that the tissue is in a dynamic rather than a static state. This “probe rejection” response involves not only humoral mechanisms but also the influx and activation of inflammatory cells (neutrophils, monocytes, macrophages, *etc.*), particularly macrophages resulting in cell activation and fibrin deposition on the probe. Figure 2 shows the contrast between an unused polyethersulfone microdialysis probe with a 3,000-kDa molecular weight cut-off (MWCO) and one removed from the human forearm 6 h after implantation. Similar findings have been reported with probes inserted into rat brain for 24 h where there was a high degree of inflammation and substantial fibrin deposits on the probe (22).

In addition, the foreign body response results in ‘tissue encapsulation’ of the probe that can affect recovery of small molecules such as glucose in unexpected ways (23). For example, Wisniewski *et al.*, using a range of commercially available microdialysis probes, each with different membrane chemistry, observed that glucose flux decreased with time in rat subcutaneous tissue (24) but increased in humans (23). For other implanted microdialysis sampling-based glucose sensors, it has been found that for longer term microdialysis probe implants, 2–3 days was necessary to achieve a stable glucose concentration (25).

Duration of implantation has also been shown to influence recovery of larger molecules such as cytokines. In studies using CMA/20 probes with PES membrane (100-kDa MWCO) in the subcutaneous space in rats, Wang *et al.* found measurable levels of IL-6 present in probes 3 and 7 days after implantation (26). At 3 days, IL-6 concentration was $470\ \text{pg/ml}$ in the first 30-min sample, while at 7 days the first aliquot had a mean concentration of $290\ \text{pg/ml}$. These IL-6 concentrations from the rat are similar to other reports from humans (16,19).

THE IMPACT OF PROBE-ASSOCIATED TISSUE INJURY ON MICRODIALYSIS SAMPLING

The Effect of the Early Phase Inflammatory Response

The primary event of the early phase inflammatory response that affects microdialysis is the local increase in blood flow, which will dramatically influence the recovery of both endogenous molecules and xenobiotics. Of particular importance to many microdialysis studies is the role that localized blood flow plays on analyte delivery to and distribution within the vicinity of the dialysis probe and how this may vary with time. Anderson *et al.* used laser Doppler perfusion imaging to determine the time course of the

Fig. 1. General time course of cytokine generation following tissue injury

perturbation of localized blood flow post-microdialysis probes insertion into the forearm skin of human volunteers (27). These studies showed that while there was an initial hyperemia, skin blood flow returned to pre-insertion levels at 60 min (27). This experimental finding has been repeated in the Clough laboratory and as illustrated in Fig. 3.

It might be anticipated that changes in local blood flow will also influence solute recovery by the probe as a result of consequential changes in the rate of clearance of the molecule of interest from the tissues. Clough *et al.* have investigated the impact of changes in local blood flow on the recovery of a small, diffusible molecule (sodium fluorescein) from the extravascular tissue space of the skin by microdialysis *in vivo*. Whereas loss of tracer from the delivery probe appeared unaffected by changes in local blood flow, recovery was directly related to blood flux manipulated using vasodilators and constrictors and measured using scanning laser Doppler imaging (28). These studies in the skin are consistent with microdialysis theory (29–32). They suggest that clearance of a small solute by the blood will have a significant impact on microdialysis probe recovery and that, in the skin, the magnitude of this clearance is directly related to blood flow (Fig. 4). In contrast, there are no studies on the impact of blood flow on local cytokine concentrations and recovery. While the influence of the diffusion of analytes in the tissue is not strictly an effect of probe insertion, it is an often-over-

looked limitation of dermal microdialysis and, thus, deserves mention in this commentary.

The impact of disruption of the tissue space, physically or as a result of local edema on the recovery of poorly diffusible molecules such as cytokines, must be taken into consideration. Studies suggest that the maximum lateral diffusion of such substances is around 2 mm under these conditions (28,33). While this apparent sampling volume may be an advantage when investigating the localization of released substances, it also means that prolonged dialysis leads to a partial depletion of dialyzable molecules in the immediate vicinity of the probes (28). Thus, although it is scientifically legitimate to cite only the analyte concentrations of interest present in the dialysate at any time, local extracellular concentrations are likely to be considerably greater.

The Effect of the Chronic Inflammatory Response

As stated above, the hallmark of the chronic inflammatory response is the generation of chemokines and cytokines. This may pose serious difficulties with respect to data interpretation in the investigation of diseases of an inflammatory nature or having an inflammatory component. In a study of the dermal allergic response, IL-6 and IL-8 were the primary cytokines released both at the allergen challenged site and the non-challenged site, the site to control for the tissue response to probe insertion (16). The cytokine responses were significantly greater at the challenged site compared with the control (Fig. 5). The recovery of IL-6 and IL-8 at the “control” site is consistent with an upregulation under wounding conditions in the skin (34,35). However, without this control site, interpretation of the cytokine response to allergen challenge would not have been possible. Even with it, we cannot rule out

Fig. 2. Scanning electron micrographs of a polyethersulfone (PES) 3,000-kDa molecular weight cut-off microdialysis probe membrane before implantation and after implantation for 6 h in human skin

Fig. 3. **a** Scanning laser Doppler images of blood flow before (a), 15 min (b), and 90 min (c) after probe insertion. *Dashed lines* indicate probe location, *white boxes* the area over which mean blood flux was calculated. **b** Mean blood flux measured over 3 h following microdialysis probe insertion. The *dashed line* represents the mean value for blood flux prior to probe insertion. Values are mean $\pm$ SEM, $n=4$

the possibility that the wounding response “primed” the surrounding tissues for an abnormal response to allergen. While the use of “control” sites is possible when studying locally initiated responses, they cannot be used for investigating systemic conditions, such as type II diabetes or obesity where only comparisons between individuals with and without disease are possible.

A further effect of chronic inflammation on microdialysis is the combination of possible biofouling of the membrane material combined with the known collagen deposition that begins to occur at approximately 5–7 days post-implantation for any implanted material. For molecules that are replenished into the tissue space via blood capillaries, the walling off with the collagen capsule appears to affect the supply to the dialysis probe and thus results in the appearance of a lower recovery for compounds such as glucose (24).

In different long-term implant studies with both polycarbonate and polyethersulfone (PES) studies with antipyrine performed by Xiaodun Mou in the Stenken group, antipyrine was locally infused through microdialysis sampling probes implanted for up to 10 days (36,37). No significant differences were observed with the delivery (extraction efficiency) of antipyrine between any of the sampling days over a 7- to 10-day period for both types of membranes. However, when an intravenous injection of antipyrine was given, there were significant differences in the recovered amounts from probes that had been acutely implanted *vs.* those implanted for 7 (PC) or 10 days (PES).¹

Similar to small molecules having their diffusive path impeded due to the foreign body reaction, Wang *et al.* have observed alterations in IL-6 collection from probes implanted acutely *vs.* those implanted for 3–7 days. In these studies, a strong cytokine response was generated by injected lipopolysaccharide. Reductions of 80% or greater in collected cytokines were observed (26). From the limited number of studies that have been performed to address these problems, it is suggested that while membrane fouling and tissue encapsulation both contribute to the reduction of dialysis efficiency, the relative contribution of tissue encapsulation is likely to be greater.

CONCLUSIONS AND ADVICE TO EXPERIMENTERS

It is evident from this discussion that the typically promoted suggestion that a microdialysis probe is a “benign” artificial capillary must be rethought. Insertion of a microdialysis probe into the skin leads to inflammatory responses, both acute and chronic, and an immunological probe rejection response, all of which have the potential to affect experimental microdialysis in different ways. Thus, when we talk of “a time allowed for the skin to recover from trauma”, this statement can only be relative and dependent on the type of study to be performed.

For the recovery of xenobiotic compounds, for example in pharmacokinetic or pharmacodynamic studies, dermal blood flow is the major dependent variable. It is essential to be aware of the impact that perturbations in blood flow have on the local concentration of xenobiotic molecules and, consequently, on their recovery from the tissue space. In this case, “tissue recovery” should be interpreted as a return to macroscopically normal blood flow. In practice, this is approximately 2 h. Furthermore, while reducing dermal blood flow by the use of a vasoconstrictor agent, such as noradrenaline, may result in increased recovery of xenobiotics, (28) it is probably inappropriate for endogenously generated molecules because of the other effects of sympathomimetics on the local environment.

¹ The Stenken group experience with microdialysis sampling probes is that polycarbonate/polyether (PC) membranes were able to function up to 7 days and PES probes to 10 days. However, PC membranes are no longer available and have been replaced with a polyarylethersulfone membrane. We have not tested the long-term implantation viability of these membranes in animals.

Fig. 4. Schematic representation of the impact of prolonged dialysis on the partial depletion of dialyzable molecules in the immediate vicinity of the microdialysis probe. Studies suggest that lateral diffusion of small solutes is around 1–2 mm (28,33)

For small molecular mass endogenous compounds, the recovery time will depend on their potential involvement in the response to tissue injury. Similarly, studies in which the targets are cytokines or molecules similarly involved in the injury response will need to incorporate into their protocols a period during which some sort of equilibration can be attained, or alternatively ensure that the intervention being studied generates the molecules of interest in quantities sufficiently larger than those released in response to probe insertion. For most endogenous molecules, recovery time is really an unknown since there are few good non-invasive

methods for measuring basal concentrations without perturbation of the tissue space.

In conclusion, when we ask the question about how minimally invasive microdialysis is, we have to answer that, like any other surgical procedures, it produces tissue injury with a consequential recovery response. However, it is less tissue disrupting than other techniques used to recover chemicals from the skin, such as skin blisters or tissue biopsies. Furthermore, it is much more acceptable for use in humans as it does not result in scarring or other cosmetic after effects. Finally, like other techniques for sampling tissue

Fig. 5. Cytokine recovery using 3,000-kDa MWCO dialysis probes from 17 healthy volunteers with a positive skin prick test to either 6-grass mix or *Dermatophagoides pteronyssinus* (house dust mite) at two sites before and following intradermal injection of either allergen or saline control. The periods of dialysate collection were: *Baseline*, the 30-min period immediately before injection of allergen or saline (control); *30 min*, the 30-min period immediately following injection of allergen or saline; *3 h*, 3–3.5 h after injection of allergen or saline; and *6 h*, 6–6.5 h after injection of allergen or saline. Bars represent median values. Data redrawn from (16)

spaces, dermal microdialysis does have its advantages, but it also has limitations of which experimenters should be aware.

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