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Journal
Experimental dermatology, 29(1)

ISSN
0906-6705

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Publication Date
2020

DOI
10.1111/exd.14055

Peer reviewed

HHS Public Access

Author manuscript

Exp Dermatol. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Exp Dermatol. 2020 January ; 29(1): 112–113. doi:10.1111/exd.14055.

Stress test of the skin: The cutaneous permeability barrier treadmill

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Abstract

Studying skin barrier function is central to our understanding of many skin disorders. The past decade has seen a surge of skin barrier related investigative work. Genetic, biochemical and cell biology experiments have added much evidence to the importance of the barrier in disease pathogenesis of a variety of disorders including ichthyosis, atopic dermatitis, and psoriasis. However, functional assays prove ever more important to demonstrate relevance of any of these findings. A paper published by Monash and Blank 60 years ago describes a stress test of the skin barrier, measuring skin barrier recovery, a functional test of tremendous implications as described in this editorial. This seminal paper has not been cited for almost 15 years, time to acknowledge its critical importance.

Keywords

Epidermis; metabolism; permeability; signaling; skin; stratum corneum

If a patient has chest pain on exertion the doctor will obtain vital signs, an ECG and blood tests. In some instances the doctor may go on to assess heart rate, blood pressure, and ECG readings during exercise. This is a measure of the heart‘s ability to respond to physical stress) in a controlled clinical environment and is called a cardiac stress or treadmill test. Importantly, the return of measurements back to normal provides information on metabolic recovery [1, 2].

Monash and Blank in 1958, in a paper entitled “Location and re-formation of the epithelial barrier to water vapor”, described how to assess stratum corneum function after applying stress to the skin barrier[3]. The stress that they applied to the skin surface was adhesive tape

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Author contribution MS, KRF and PME designed and wrote the manuscript cooperatively.

Conflict of interests

The authors have declared no conflicting interests.

stripping. The read out was a change in physiologic water evaporation through the skin (perspiration insensibilis) measured as trans epidermal water loss (TEWL).A second read out was the time required for 2%lidocaine to exert topical anesthesia. While the data in this paper were primarily devoted to generating evidence for arguing with Stephen Rothman about whether the stratum corneum accounts for the barrier to insensible water loss or not[4], their stress test provided an important measure for the ability of the epidermis to restore the barrier. Thus, the authors established a functional in vivo test to predict the ability of the skin to recover from external, physical stress, i.e. a cutaneous treadmill test.

Since its initial description, this test has been widely used. 1) The recovery of barrier function has been proven very useful to better understand the various metabolic changes that are required for barrier repair. For example, if one inhibits cholesterol synthesis, barrier recovery is delayed [5, 6]. Restoration of barrier functionhas been an essential technique for understanding the various factors that play key roles in the formation and maintenance of the barrier. This has provided great insights into the pathways of barrier repair [7]. 2) Barrier recovery measurements have been used to uncover underlying developmental differences or pathology that is not detected by assessment of basal function (which is often misleading) as in aged, neonatal, darkly- vs. lightly pigmented skin, psychologically-stressed, glucocorticoid-treated; and testosterone-replete vs. deficient individuals [7–12]. 3) The test has also been used to compare the efficacy of putative ‘barrier repair’ therapies (do they accelerate or delay barrier recovery?); and 4) to assess the efficacy of metabolically based penetration enhancers (‘how effectively do they open the window, and can they ‘prolong the window’?).

The test cannot only be applied to human skin, but also to animal or in vitro models of skin[13]. Depending on the experimental model used and the scientific question asked, alternate forms of external stress can be applied, e.g. instead of tape stripping a detergent such as sodium dodecyl sulfate can be applied to the stratum corneum, which depletes lipids and thereby acutely increases TEWL[11]. Furthermore, the external stress can be afflicted to the skin either in an acute or in a chronic setting[14–16]. Taken together, by establishing a proof of concept, Monash and Blank laid the groundwork for testing of skin barrier repair. This dynamic test nicely complements current uses of tape stripping under steady-state conditions[17–18].

Skin barrier recovery testing has limitations that the reader should be aware of. TEWL is only a surrogate marker for the inside-outside barrier. It does not solely depend on stratum corneum function, but it also varies with skin temperature and blood flow[19]. Therefore, such stress test in vivo and in vitro is significantly different. Furthermore, measuring TEWL can be biased by environmental factors, which should be carefully controlled and monitored (relative humidity, atmospheric pressure, room temperature)[20]. To be less dependent on environmental conditions influencing TEWL measurements, Monash and Blank also measured the restoration of skin permeability to a topical anesthetic, lidocaine, as described above. Today’s investigators, 60 years later, may reconsider using this alternate read out in barrier recovery experiments.

Other limitations of recovery testing include inter-individual variations of the skin's homeostatic response to standardized external assaults. Variable response to the same amount of tape stripping has to be accounted for in designing barrier recovery experiments. Rather than using a constant number of tape strippings to exert maximal stress, it may be necessary to define a relative measure, e.g. a 6-fold increase above baseline TEWL as maximal stress, which will then allow for a more meaningful interpretation of recovery kinetics.

Importantly, recovery measurements of diseased skin have to be interpreted with caution, because repair kinetics may be significantly altered due to increased baseline TEWL and related metabolic processes. Studies have shown that barrier recovery actually accelerates in atopic dermatitis. This apparent paradox can be explained as follows: There is a barrier abnormality even in non-lesional skin, so metabolic processes are continually upregulated; i.e., there is no delay in recovery kinetics, because of an ongoing attempt by the epidermis to repair the defect. Yet, the epidermis is unable to completely restore the barrier.

Taken together, describing the kinetics of reformation (recovery) of the epithelial barrier after experimental disruption has provided us with a powerful tool to assess the permeability barrier function of the skin and thus was a seminal discovery.

Funding

This work was supported in part by National Institute of Health (NIH) Grant AR061106 to PME, Austrian Science Fund (FWF) I 4229 to MS, and the Walter Schaar Foundation.

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