New and Notable

Low Voltage Electroporation of the Skin, or Is It Iontophoresis?

Sek Wen Hui
Biophysics Department, Roswell Park Cancer Institute, Buffalo, New York 14263 USA

The skin is an effective barrier against toxic chemicals and pathogens. Its uppermost layer, the stratum corneum, is composed of layers of corneocytes and lipid multilayers and is impermeable to most water soluble substances. It also constitutes a formidable obstacle to transdermal delivery of drugs and genetic materials. The transdermal route, if available, provides an alternative, convenient, and noninvasive pathway for local and systemic delivery, especially with regard to timed release and the avoidance of degradation or metabolism in the gastrointestinal tract or liver. The stratum corneum is crossed by many appendages such as hair follicles and sweat glands. The lining of these appendageal ducts, consisting of two layers of epithelial cells, is much less resistant than the stratum corneum to drug transport.

Many biophysical approaches have been made to facilitate the transport of selected chemicals across the skin barrier. The most well known method is iontophoresis. In this approach, a low DC voltage (normally <5 V) is applied across the skin. Charged molecules to be delivered are placed under an appropriate electrode and are driven through the skin barrier by electrophoresis and electroosmosis (Oh et al., 1993; Cullander, 1992). The transport passage is believed to be mainly through the appendages. The electrical impedance spectra of the skin are well characterized, and the transport by iontophoresis has been analyzed by macroscopic theory (Edwards and Langer, 1994).

About 20 years ago, reversible electroporation of biological membranes was recognized as a means to deliver materials into living cells (Chang et al., 1992). This method is based on the resilience of the cell membrane to reseal after a temporary electric breakdown. Dielectric breakdown of a lipid bilayer and a cell membrane is reached at a transmembrane potential of about 0.5 and 1 V, respectively (Abidor et al., 1979; Benz et al., 1979; Neumann et al., 1982; Zimmermann, 1986; Tsong, 1987; Stenger et al., 1991). Because of the low electric conductivity across the membrane, as compared with those of the cytoplasm and the external media, the major potential drop across the cell is concentrated across the plasma membrane "poles" facing the electric field direction. This leads to the electroporation of the membrane, whereas the rest of the cell experiences a much lower potential gradient. The same advantage applies to the electroporation of the skin barrier in which the major potential drop develops across the highly resistive stratum corneum, the target for electroporation. This was recognized recently, and the technique has been applied, although sometimes in an irreversible sense, to permeabilize the skin for drug delivery purposes (Prausnitz et al., 1993; Vanbever et al., 1994). For short term permeabilization of the skin, a pulse of 20–40 V across some 70–100 lipid bilayers in the stratum corneum (about 250–500 mV/bilayer) is sufficient (Pliquett et al., 1995; Gallo et al., 1997). To achieve a prolonged electrical permeabilization of the stratum corneum, a pulse voltage exceeding a threshold of about 75 V (1 V/bilayer), is required (Prausnitz et al., 1993; Vanbever et al., 1994; Gallo et al., 1997). This threshold agrees with that measured for the electrical breakdown of lipid bilayers and cell membranes (Edwards et al., 1995; Chizmadzhev et al., 1995).

A paradox is realized that, if electroporation occurs when a potential of 1 V is applied across a cell membrane, the membranes of the epithelial cell layers lining the skin appendages are porated as soon as the low iontophoretic voltage (>4 V) is applied to the skin. The molecular transport by iontophoresis should then be considered as the consequence of electroporation of the epithelial layers of the skin appendages. This alternative interpretation is complicated by the fact that the potential drop along narrow hair follicles or sweat glands must also be taken into account in calculating the net potential drop across the epithelial cell layers at different depths from the skin surface. Furthermore, the response and resealing times of the membrane to the applied electric field are unknown, adding to the difficulty in modeling the low field electroporation if a pulse or AC voltage is applied in the traditional iontophoretic setting (Gallo et al., 1997).

This problem is now considered in detail by Chizmadzhev et al. (1997) in this issue. They present a simple geometric model for the appendages with its equivalent circuit. After an elegant classical analysis, they derived the potential along the appendageal tube at given times after the initiation of the pulse and the development of electropores manifesting as the decrease of electric resistance. The calculation, using realistic parameters for skin tissues, matches well with the steady state and time-resolved measurements of the current-voltage characteristics reported previously and in this paper. Furthermore, with increasing applied voltages, electroporation of the stratum corneum occurs and becomes the major transport pathway in place of the appendageal route. The reconciliation of the two electroporation pathways is shown as closely matched theoretical and experimental curves spanning a wide voltage range.

Received for publication 19 September 1997 and in final form 4 November 1997.

Address reprint requests to Dr. S.W. Hui, Membrane Biophysics Laboratory, Roswell Park Cancer Institute, Buffalo, NY 14263. Tel.: 716-845-8595; Fax: 716-845-8683; E-mail: roswhui@acsu.buffalo.edu.

0006-3495/98/02/679/02 $2.00

The analyses and the experimental support given in this paper provide us with a broad picture of what happens when a low electric voltage is applied to the skin with appendages. The initial event, characterized by the charging of the skin capacitor and the subsequent poration of the appendages lining, is clearly depicted. It bridges the gap between the theories of iontophoresis and electroporation. This work paves the ground for the future development of combined high and low voltage protocols designed to enhance the transdermal transport, which will play an increasingly important role in drug and gene delivery.

REFERENCES

Abidor, I. G., V. B. Arakelyan, L. V. Chernomodik, Yu. A. Chizmadzhev, V. F. Pastushenko, and M. R. Tarasevich. 1979. Electric breakdown of bilayer lipid membranes. *Bioelectrochem. Bioenerg.* 6:37–52.

Benz, R., F. Beckers, and U. Zimmermann. 1979. Reversible electrical breakdown of lipid bilayer membranes: a charge-pulse relaxation study. *J. Membr. Biol.* 48:181–204.

Chang, B. M., J. A. Chassy, A. E. Saunders, and Sowers, editors. 1992. Handbook of Electroporation and Electrofusion. Academic Press, New York.

Chizmadzhev, Yu. A., A. V. Indenbom, P. I. Kuzmin, S. V. Gallchenko, J. C. Weaver, and R. O. Potts. 1997. Electrical properties of skin at moderate voltages: contribution of appendageal macropores. *Biophys. J.* 74:843–856.

Chizmadzhev Yu. A., V. G. Zarnitsin, J. C. Weaver, and R. O. Potts. 1995. Mechanism of electroinduced ionic species transport through a multilamellar lipid system. *Biophys. J.* 68: 749–765.

Cullander, C. 1992. What are the pathways of iontophoretic current flow through mammalian skin? *Adv. Drug Delivery Rev.* 9:119–135.

Edwards, D. A., and R. Langer. 1994. A linear theory of transdermal transport phenomena. *J. Pharm. Sci.* 83:1315–1334.

Edwards, D. A., M. R. Prausnitz, R. Langer, and J. C. Weaver. 1995. Analysis of enhanced transdermal transport by skin electroporation. *J. Controlled Release.* 34:211–221.

Gallo, S. A., A. R. Oseroff, P. G. Johnson, and S. W. Hui. 1997. Characterization of electric pulse induced permeabilization of porcine skin using surface electrodes. *Biophys. J.* 72: 2805–2811.

Neumann, E., M. Schaefer-Ridder, Y. Wang, and P. H. Hofschneider. 1982. Gene transfer into mouse lyoma cells by electroporation in high electric fields. *EMBO J.* 1:941–945.

Oh, S. Y., L. Leung, D. Bommannan, R. H. Guy, and R. O. Potts. 1993. Effect of current, ionic strength and temperature on the electrical properties of skin. *J. Controlled Release.* 27: 115–125.

Pliquett, U., R. Langer, and J. C. Weaver. 1995. Changes in the passive electrical properties of human stratum corneum due to electroporation. *Biochim. Biophys. Acta.* 1239:111–121.

Prausnitz, M. R., V. G. Bose, R. Langer, and J. C. Weaver. 1993. Electroporation of mammalian skin: a mechanism to enhance transdermal drug delivery. *Proc. Natl. Acad. Sci. USA.* 90:10504–10508.

Stenger, D. A., K. V. I. S. Kaler, and S. W. Hui. 1991. Dipole interactions in electrofusion: contributions of membrane potential and effective dipole to interaction pressure. *Biophys. J.* 59:1074–1084.

Tsong, T. Y. 1987. Electric modification of membrane permeability for drug loading into living cells. *Methods Enzymol.* 149:248–259.

Vanbever, R., N. Lecouturier, and V. Preat. 1994. Transdermal delivery of metoprolol by electroporation. *Pharm. Res.* 11:1657–1662.

Zimmerman, U. 1986. Electrical breakdown, electropermeabilization and electrofusion. *Rev. Physiol. Biochem. Pharmacol.* 105: 175–256.