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Preface

Enhanced drug delivery using high-voltage pulses

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Successful delivery of drugs into the body and to target tissues and cells inside is limited largely by slow transport across biological barriers, mostly in the form of lipid bilayer membranes. Although transdermal drug delivery has found success for a handful of small compounds, the poorly-permeable lipid bilayers in skin's stratum corneum prevent therapeutic delivery of most drugs, especially macromolecules. Similarly, targeted delivery of drugs to tissues (e.g., tumors) and into cells (e.g., for gene therapy) is blocked by lipid bilayer cell membranes. Drugs and genes which could selectively cross cell membranes could be targeted to cells and tissues of interest.

Application of short, high-voltage pulses provides a way to reversibly disrupt lipid bilayer membranes, thereby creating pathways to deliver molecules across cell membranes, into tissues and through the skin by a mechanism commonly called electroporation. By briefly inducing a transmembrane voltage of a few hundred millivolts, lipid bilayers are known to become permeable within microseconds and then reseal within seconds to minutes. As a well known method for laboratory DNA transfection of cells, electroporation has recently been applied to tissues and shown to reversibly permeabilize them, often without loss of viability. Electroporation-mediated drug delivery can provide a way to increase drug and gene transport across these biological barriers which limit transdermal and targeted delivery.

One promising application of tissue electroporation is transdermal drug delivery, which is believed to involve transient disruption of lipid bilayer structure within the skin's stratum corneum. Application of high-voltage pulses to the skin has been shown to increase transdermal drug delivery by several orders of magnitude, both in vitro and in vivo. Controlled rates of delivery can be achieved by modifying electrical parameters and drug formulation. Experimental data suggest that skin electroporation could provide a drug delivery method that is both safe and effective.

Another promising application of tissue electroporation is electrochemotherapy. It consists of applying high-voltage pulses to permeabilize tumor cells to a non-permeant drug (e.g., bleomycin). In this way, only cells exposed to high-voltage pulses take up sufficient drug to be affected. Using this targeting mechanism, skin, liver and other tumors have been eradicated in animal models and recent clinical studies show promising results. By a similar method, in vivo gene therapy has been demonstrated using high-voltage pulses to different tissues in animals.

This issue of Advanced Drug Delivery Reviews summarizes the current status of high-voltage pulsing for drug delivery applications. After an introductory paper on cell electroporation, a series of papers

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discuss theoretical and experimental studies of skin electroporation, including mechanistic, delivery and safety issues. The final papers address electroporation of tissues for enhanced cancer chemotherapy and gene delivery. Combined, these studies indicate that high-voltage pulsing can be an effective way to increase lipid bilayer permeability and thereby enhance and target delivery of drugs and genes.