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Original article

Dermal/transdermal delivery of small interfering RNA and antisense oligonucleotides- advances and hurdles

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ABSTRACT

A diverse array of nucleic acids has been studied by several researchers for the management of several diseases. Among these compounds, small interfering RNA and antisense oligonucleotides have attracted considerable attention. Antisense oligonucleotides are synthetic single stranded strings of nucleic acids that bind to RNA and thereby alter or reduce expression of the target RNA while siRNAs, on the other hand, are double-stranded RNA molecules which can hybridize with a specific mRNA sequence and block the translation of numerous genes. One of the main obstacles in the dermal or transdermal delivery of these compounds is their low skin permeability. In this review, various techniques used to enhance the delivery of these molecules into or across the skin are described and in some cases, the correlation between enhanced dermal/transdermal delivery and therapeutic efficacy is highlighted.
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1. Introduction

There are significant hurdles relating to the dermal/transdermal delivery of antisense oligonucleotides and small interfering RNA. However, advances are being made by researchers to enhance the dermal/transdermal delivery of these compounds. Antisense oligonucleotides (ODN) and small interfering RNA (siRNA) must cross barriers and enter into the cytoplasm in order to interact with mRNA [1]. It is, however, important to note that nucleic acids (NAs) have negative charge and therefore the transport of these compounds across cell membranes is limited [1].

The poor delivery of siRNA, antisense ODN and decoy ODN is attributed to limited skin penetration due to the high ionization, low lipophilicity, and high molecular weight of these molecules [2]. An interesting approach is the decoy method which leads to

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the modulation of endogenous transcriptional regulation [2]. Morishita and coworkers had earlier observed that the transcriptional factor nuclear factor-kappaB (NF-κB) plays an important role in the transactivation of cytokine and adhesion molecule genes involved in myocardial damage and that synthetic double-stranded DNA with high affinity for NF-κB could be introduced in vivo as "decoy" cis elements to interact with the transcriptional factor and subsequently antagonize the activation of these genes [3]. This approach was later used by Hashim et al. who hypothesized that the skin's allergic response in atopic dermatitis might be improved by the transfection of NF-B decoy ODN [2].

RNA interference (RNAi) represents a conserved gene silencing approach in which double strand RNA (dsRNA) is used as a signal to trigger the degradation of complementary mRNA sequences [4]. The design of siRNA duplexes capable of interfering with the expression of a specific gene can be carried out with the knowledge of at least a 20-nt segment of its encoded mRNA [5]. RNAi is widely used for gene silencing and drug development because of its high specificity, significant effect, minor side effects and ease of synthesis [6].

The following classes of antisense oligonucleotides (ASOs) have been identified: RNase H-dependent ASOs, exon-skipping ASOs, siRNAs, anti-microRNA (anti-miRs) and microRNA (miRNA) mimics [7]. RNase H-dependent antisense oligonucleotides (ASOs) bind to complementary sequences in target mRNAs and reduce gene expression both by RNase H-mediated cleavage of the target RNA and by inhibition of translation by steric blockade of ribosomes [7]. Exon-skipping ASOs are single-stranded, chemically modified ASOs that target intron–exon junctions (splice sites) or splicing-regulatory elements [7]. Small interfering RNA (siRNAs) are double-stranded RNA molecules with each strand consisting of 21–23 nucleotides, 7.5 nm long and 2 nm in diameter [8]. Oligonucleotides can be used to antagonize (in which case they are known as anti-miRs) or mimic the function of endogenous microRNAs (miRNAs) [7].

RNAi involves the cleavage of double-stranded RNAs by the cellular nuclease Dicer into short 21–22 mer fragments referred to as siRNA, which enter a ribonuclear protein complex called the RNA-induced silencing complex(RISC) [9]. Because the rational design of siRNA can specifically block endogenous and heterologous gene expression, it can be used to modulate any disease-related gene expression [6].

RNAi offers the possibility of targeting and silencing any pathological protein in a specific way and the process is mediated endogenously by microRNAs (miRNAs) and experimentally by small interfering RNAs (siRNAs) [10]. Both sets of molecules are small (~22 nt) noncoding RNAs that, once loaded into the cytoplasmic RNA-induced silencing complex, bind to their target messenger RNA (mRNA) and block translation [10]. This leads to the inhibition of gene expression [10]. There have been significant advances resulting in successful clinical trials [11].

siRNAs are capable of hybridizing with a specific mRNA sequence and blocking the translation of numerous genes [12]. There are ongoing efforts on the use of chemically synthesized small RNAs designed to manipulate miRNA expression [11]. Generally, RNAi includes the use of short double or single stranded oligonucleotides, which inhibit gene expression through specific pathways [13]. These include endogenous microRNAs, small interfering RNA (siRNA), short hairpin RNA (shRNA) and antisense oligonucleotides (ASOs) [13]. Piwi-interacting RNAs (piRNAs), another class of small RNA molecules, form RNA-protein complexes through their affinity with Piwi proteins [13]. piRNAs are generally 24–32 nucleotides (nt) in length and bind specifically to the PIWI subfamily of Argonaute proteins [14]. Piwi was first found in *Drosophila*, in which it is required for the asymmetric division of germline-stem cells [14].

Antisense oligonucleotides (AS-ODNs), are synthetic single-stranded DNA fragments capable of interacting with specific intracellular messenger RNA strands (mRNA) to form a short double helix [15]. These synthetic single stranded strings of nucleic acids, between 8 and 50 nucleotides in length, bind to RNA through the standard sequence-specific Watson–Crick base pairing and sterically block the translation of this transcript into a protein [16,17]. AS-ODNs comprise short sequences which are complementary to mRNA strands in a region of a coding sequence designed as sense strand [15]. Antisense oligonucleotides can alter RNA function through different mechanisms [16]. They can be used to restore protein expression, reduce expression of a toxic protein, or modify mutant proteins to reduce their toxicity [16]. AS-ODNs modulate RNA function by degradation of the target RNA by the enzyme, RNase H, or modulation of RNA intermediate metabolism such as splicing [18]. In 2013, the FDA approved mipomersen, an antisense oligonucleotide which targets ApoB100 for the treatment of homozygous familial hypercholesterolaemia (HoFH), a rare genetic disorder which leads to excessive levels of low-density lipoprotein (LDL) cholesterol [19].

MicroRNAs (miRNAs) are endogenous, noncoding RNAs that have been identified as post-transcriptional regulators of gene expression [20]. miRNAs negatively regulate gene expression, mainly through direct interaction with the 3′ untranslated region (3′-UTR) of corresponding target messenger RNAs (mRNAs) [20].

The skin limits the amount of therapeutic agents that can be delivered into the human body. The main berrier is provided by the stratum corneum-the outermost layer of the skin. Drug delivery scientists have developed an avalanche of techniques to overcome the skin barrier. Iontophoresis, sonophoresis, microneedles, lipid nanocarriers, peptide enhancers, lipoplexes, spherical nucleic acid nanoparticle conjugates and chemical penetration enhancers are some of the approaches used. Iontophoresis involves the use of mild electric current to drive ionized and neutral molecules across the skin [21]. Electromigration and electrosmosis are the main transport mechanisms in iontophoresis [22]. The experimental setup for iontophoresis is shown in Fig. 1. The charged molecule, is placed under one or both electrodes such that electrorepulsive forces drive the molecule away from the electrode, into the skin [23]. A positively charged drug is placed under the positive electrode or anode, while a negatively charged drug is placed under the negative electrode or cathode [23]. Positively charged cations are repelled by the anode while negatively charged anions are repelled by the cathode into the skin [24]. In the case of neutral molecules, the convective movement of water (electrosmosis) becomes the principal transport mechanism [25]. In practice, a current controller (Fig. 2) is used to deliver current to the skin [23].

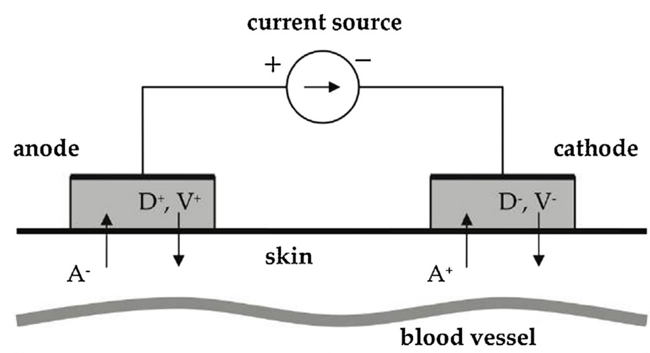

Fig. 1. Schematic representation of transdermal iontophoresis. D+ and D− are positively and negatively charged drug ions, respectively. V+ and V− are positively and negatively charged co-ions in the drug solution. A+ and A− are counter-ions traveling from the skin towards the electrode to maintain electroneutrality. (Reproduced with permission from Ref. [23]).

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