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## DERMATOLOGY | RESEARCH ARTICLE

# Proposed mechanism of action of tap water iontophoresis for treatment of hyperhidrosis

Blaine D. Griffen<sup>1\*</sup>

**Abstract:** Tap water iontophoresis is commonly used to treat hyperhidrosis, yet the mechanism of action for this treatment remains unknown. Here, I propose a plausible mechanism of action based on the biology of the eccrine sweat gland, reported patterns in iontophoresis effectiveness, and known dynamics of small particles in fluid systems. Specifically, I propose that iontophoresis works via the production of a colloid formed between the products of dark (mucin) and clear (aqueous solution) cells, and the jamming of nanomineral particles inside the lumen and/or the duct of the sweat gland, creating a blockage that temporarily prevents further sweat production or secretion. I further outline several feasible tests of this hypothesis.

**Subjects:** Chemistry; Applied Physics; Physiology; Cosmetic Dermatology

**Keywords:** colloid; hyperhidrosis; iontophoresis; mineral nanoparticles; particle jamming; tap water

### 1. Introduction

Hyperhidrosis affects 1–3% of the population (Quraishy & Giddings, 1993; Walling & Swick, 2011) and can hamper social and professional interactions (Christopoulos, 2004). The precise cause of the condition is not fully understood, though the prevalence of hyperhidrosis within families suggests a genetic component (Ro, Cantor, Lange, & Ahn, 2002). Several treatments have been used to control excessive sweating. One of the primary treatments that has been used since 1952 is tap water iontophoresis (Bowman & Lentzer, 1952). (See Pariser and Ballard (2014) for a thorough description of iontophoresis.) Despite its widespread use, this treatment is not universally effective and, even in cases where it does work, its effects are often only partial and inconsistent

### ABOUT THE AUTHOR

This work represents a departure from the normal research direction of the author and his research group, which generally focuses on ecological questions related to human disturbance of the environment. The current project reflects the broad training, interests, and thinking of the author across the biological and physical sciences.

### PUBLIC INTEREST STATEMENT

Excessive sweating of the hands and feet affects up to 3% of the population. One of the primary treatments for this condition involves placing the hands or feet into a water bath and passing mild electrical current through the water, a procedure known as tap water iontophoresis. While this treatment is widely used, it is often not completely effective. To date, it is not known why this treatment stops excessive sweating. Improving the effectiveness of the treatment therefore requires understanding of how or why it works in the first place. This article proposes a hypothetical mechanism by which tap water iontophoresis may reduce sweating. Providing this hypothesis is intended to stimulate further research and experimental work in the hopes of improving the effectiveness of this treatment.

(Gordon & Maibach, 1969; Holze & Ruzicka, 1986). Several hypothesized mechanisms of action have been proposed for this treatment, including the reversible disruption of ion channels (Collin & Whatling, 2000), dermal injury resulting in abnormal keratinization and plugging of the sweat duct (Gordon & Maibach, 1969; Shelley & Horvath, 1950), blockage of neuroglandular transmission (Holze & Ruzicka, 1986), or inhibition of the secretory mechanism at the cellular level. However, studies to date have failed to reveal changes in the eccrine sweat glands or blockages of sweat ducts following iontophoresis (Hill, Baker, & Jansen, 1981; Holze & Ruzicka, 1986), and thus fail to support these hypothesized mechanisms. A lack of understanding of the mechanism of action for this treatment hampers developing improved techniques to enhance the effectiveness of the treatment. Here, I propose a mechanism of action that is consistent with what is known about the function of eccrine sweat glands and with known physical, chemical, and biological processes. Below, I provide brief background on several topics, touching only on those aspects that are necessary to inform the proposed mechanism.

## 2. The eccrine sweat gland structure and function

Eccrine glands are composed of a lower secretory coil and a duct that leads to the surface of the skin. The most restrictive portion of this structure is the duct leading to the dermal surface, which has a lumen diameter of just 10–15  $\mu\text{m}$  (Bovell, 2015).

The secretory portion of the gland includes dark cells and clear cells, along with myoepithelial cells. Dark cells secrete sialomucin, an acidic glycoprotein that is a precursor of mucin (Constantine & Mowry, 1966; Munger, 1961), which, when combined with water, produces mucus. However, the specific function of the dark cells remains somewhat enigmatic, relative to the well-known secretory function of the clear cells (Bovell, 2015), though it appears that a key facet of sweat production is the release of mucopolysaccharide into the lumen of the gland by dark cells via secretory vacuoles (Munger, 1961). Examination of sweat glands following activation (both those from individuals experiencing hyperhidrosis and those experiencing normal sweat levels) revealed considerable cellular debris in the lumen of the duct, including lipid droplets (Bovell, Clunes, Elder, Milsom, & Jenkinson, 2001). At the same time, dark cells had been degranulated, indicating release of lipid-containing vacuoles. Individuals with anhidrosis and hypohidrosis have eccrine glands with degranulated and shrunken dark cells (Sano et al., 2017), highlighting the importance of dark cell function, and particularly mucin secretion, for normal sweat function. While mucin secretion by dark cells appears to be an integral component of sweat production, the bulk of the sweat production is attributable to the clear cells that secrete water-containing solutes into the lumen (Munger, 1961). Indeed, recent work concludes that clear cells are responsible for the excess secretions characteristic of hyperhidrosis (Bovell et al., 2011).

## 3. Mucin

At pH of 6–7, mucin exists as a hydrophilic protein that readily combines with water, but as the pH drops, mucin begins to aggregate because of the breakdown of salt bridges that expose hydrophobic regions of the protein, causing it to reach a gel-like state at pH 4 (Bansil & Turner, 2006).

## 4. Colloids

From the Oxford Dictionary (<https://en.oxforddictionaries.com/definition/colloid>, 2018, April 22), a colloid is a homogeneous, noncrystalline substance consisting of large molecules or ultramicroscopic particles of one substance dispersed through a second substance. Colloids include gels, sols, and emulsions; the particles do not settle and cannot be separated out by ordinary filtering or centrifuging like those in a suspension.

## 5. Tap water iontophoresis

The effectiveness of iontophoresis depends on the mineral content of the water, and generally requires several repeated treatments over a short interval before a reduction in sweating is achieved, followed by a less frequent maintenance schedule (Pariser & Ballard, 2014). Conceptually, effects could last indefinitely with periodic repeated treatments; however, in

practice, treatments are often effective for a period, but gradually become less effective. When this occurs, the process can be restarted, but generally only after a waiting period of several weeks or months, allowing full sweat production to first resume. While this pattern has not, to my knowledge, been discussed in the medical literature, it has been highlighted extensively in online discussion forums dedicated to the treatment of hyperhidrosis, with many patients finding reinitiation of treatment to be completely unsuccessful prior to a sufficient waiting period (see Hyperhidrosis Network, [socialphobiaworld.com](http://socialphobiaworld.com), [Excessive-Sweating.net](http://Excessive-Sweating.net), and others).

During iontophoresis, hydronium and hydroxide ions build up near the anode and cathode, respectively. Hydronium ions subsequently reduce the pH well below 4 in the cutaneous and subcutaneous tissue (Ledger, 1992), often causing burns and blistering when the pH drops below 4 (Schwarz & Sutcliffe, 1968).

### 6. Nanominerals and mineral nanoparticles

Nanominerals are those that only exist in the nanoparticle size, while mineral nanoparticles are those that can be <1 nm diameter but can also exist at larger sizes as well (this includes most known minerals). Both of these are widely dispersed in the atmosphere, oceans, groundwater, and surface water (Hochella et al., 2008). Krasovskii et al. (Krasovskii et al., 2010) tested natural mineral waters from different sources and found that the range and distribution of nanoparticle sizes varies considerably across waters from different sources, with peak particle sizes ranging from ~1 nm to >200 nm.

### 7. Particle jamming

Nanoparticles will spontaneously adhere to the interface between two immiscible substances, like oil and water (i.e., self-assembly), as long as the process is thermodynamically feasible (Dinsmore et al., 2002). This process occurs spontaneously because the process minimizes the Helmholtz free energy (Lin, Skaff, Emrick, Dinsmore, & Russell, 2003). Even when this process does not happen spontaneously, the process can be driven by the application of an electrical current (Lin et al., 2005; Yeh, Seul, & Shraiman, 1997). Attached nanoparticles form a monolayer at the interface of droplets that can be stable for days. Particle size is important for determining the time until particles desorb from the interface. Particles on the order of ~5 nm will remain stable for days at a time (Lin et al., 2005, 2003).

Nanoparticles on the surfaces can become jammed when a large number of particles pack closely together. This process increases the stability of the colloid and can even maintain the droplets in nonspherical shapes. In this case, the composite material acts as a solid because it is jammed and so remains in a nonfluid shape. This property has the potential to be used in a wide range of physical and biological systems, and is maintained by interfacial jamming (Subramaniam, Abkarian, Mahadevan, & Stone, 2005). This process can work with a range of sizes of particles and even with fluids that are miscible, so long as a force is applied that separates the fluids, such as an electrical current. The phenomenon is not permanent because the particles do not have equal affinity for the two liquids (known as non-neutral wetting) (Stratford, Adhikari, Pagonabarraga, Desplat, & Cates, 2005).

Further, when an external electrical field is applied to a liquid domain that includes two immiscible or miscible fluids, it causes deformation that increases the surface area of the interface between the two fluids, allowing more nanoparticles to adsorb to the interface. When the field is removed, the interfacial area decreases, naturally attempting to return to the spherical shape to minimize interfacial area and thus the interfacial energy. This causes particle jamming of the nanoparticles, thereby arresting further shape change. However, the nanoparticles remain liquid-like, enabling multiple, consecutive deformation, and jamming events (Cui, Emrick, & Russell, 2013). Cui et al. (2013) demonstrate several other properties, including that the degree of deformation depends on strength of the applied field (demonstrating increased surface area by a factor of 5 at 4.6 kV/cm), that the deformed shape was maintained for up to a month, that deformation

increased asymptotically with time that the electrical field was applied up to 15–20 min, and increased with the strength of the field, that a pulsed electric field that oscillated the current worked best, and that the greatest particle jamming was seen when nanoparticles were used that bonded together (increased duration of effect).

### 8. Proposed mechanism of action

Here, I propose the following mechanism of action of iontophoresis for treating hyperhidrosis. While, to my knowledge, no part of this hypothesized mechanism has been tested, it is entirely based on the dynamics summarized above, and each part of the mechanism has therefore previously been demonstrated. I hypothesize that the iontophoresis current causes acidic conditions inside the lumen of the eccrine duct, causing the secreted mucin to form into a gel. The gelled mucin and the aqueous secretions from the clear glands then form a colloid in the lumen and/or the duct, and mineral nanoparticles self-aggregate along interfaces of this colloid. The electrical current simultaneously enables the formation of this colloid and distends the interface between individual molecules and particles, increasing the surface area for nanoparticle attachment and particle jamming. Jammed colloid portions then clog up the eccrine ducts or perhaps just fill up the lumen and never make it to the ducts. The effects of iontophoresis wear off as the nanoparticles detach from the surfaces of the colloid, freeing the mixture to flow through the duct. Finally, I hypothesize that this process inhibits further mucin secretion, and iontophoresis does not work for some time after the effect wears off because it takes some time for dark cells to resume mucin secretion. It should be noted that the components of this mechanism are not all mutually dependent, and not all are required for the general concept to be feasible.

### 9. Possible tests of this mechanism

The mechanism described above may be experimentally examined using several approaches that test different facets of the hypothesis. For instance, since acidic conditions are required for the conversion of mucin into a gel that is required for colloidal formation, a buffer could be added to the water used in iontophoresis treatments. Reduced effectiveness of treatment using buffered water compared to unbuffered water would support the proposed hypothesis. Similarly, colloidal formation could be experimentally inhibited with the addition of surfactants to the treatment water. Reduced treatment effect with the addition of a surfactant would also support the proposed hypothesis. While these experimental treatments may weaken the effect, they may not be expected to eliminate the effect altogether, since particle jamming can occur in miscible fluids, and thus a colloid is not required for particle jamming to occur (Stratford et al., 2005). The proposed mechanism could also be experimentally tested by attempting to strengthen or prolong its effect. For instance, experimental treatments that may enhance the drying effect include adding mineral nanoparticles of a larger size and/or that form bonds. Both of these options should serve to stabilize the particle jamming and thus enhance the effectiveness of treatment.

### 10. Discussion

The mechanism proposed here should not be readily visible with light microscopy, since the lumen is being plugged with the very substances that are naturally secreted into the lumen by the sweat gland itself, explaining why previous studies found no change in the sweat duct before vs. after treatment (Hill et al., 1981). It may, however, be possible to visualize jammed nanoparticles within the lumen of the duct, if they exist, using *ex situ* electron microscopy, atomic force microscopy, or X-ray scattering (Lin et al., 2005). The mechanism that I have proposed is, admittedly, rather complicated. Occam's razor requires that simpler explanations be accepted over more complicated explanations. As indicated above, studies have failed to support previous simpler explanations, and each of the individual biological, chemical, and physical components of the proposed mechanism have been thoroughly demonstrated more generally, and it is only their individual and combined application to the effects of iontophoresis that remain untested.

Iontophoresis does not have an immediate effect from the first treatment, but generally requires an initial buildup period that fairly suddenly takes effect after several treatments. This is consistent

with the fact that multiple applications of electrical current will repeatedly deform colloid particles, facilitating the aggregation of nanoparticles at the interface required for particle jamming (Cui et al., 2013). Further, without periodic treatments, the drying effect generally wears off within a matter of days. This is consistent with the natural separation of nanoparticles from the interface that occurs, dependent on the size of the nanoparticles, over a period of days (Lin et al., 2005). Thus, the mechanism proposed here is based on well-established biological, chemical, and physical processes that are consistent with the patterns observed in the effects of tap water iontophoresis for the treatment of hyperhidrosis.

The mechanism proposed here need not act in isolation and may, in fact, combine with other potential factors. For instance, increased hydration of the stratum corneum decreases sweating (Peiss, Randall, & Hertzman, 1956); hence the observation that skin occlusion that increases dermal hydration also leads to temporary reductions in sweating (Zhai & Maibach, 2001). Reduced sweating of hydrated tissues may be due to swelling of the stratum corneum cells to provide a physical barrier that restricts the eccrine ducts as they traverse this layer on their way to the dermal surface (Peiss et al., 1956). Similar hydration of the stratum corneum may occur during tap water iontophoresis, and while this effect of hydration is generally short-lived (< 2 h), it may combine with the mechanism proposed here to limit sweating following tap water iontophoresis. If this is the case, it may explain the removal of anhidrosis following stripping of the stratum corneum (Gordon & Maibach, 1969).

Tap water iontophoresis has been used to treat hyperhidrosis for more than a half century, without substantial improvements to the procedure other than the development of convenient electrical devices for administering the treatment. Improving a treatment without first understanding the underlying mechanism relies on luck or serendipity. The introduction of a feasible mechanism here is meant to stimulate progress by highlighting scientifically likely avenues for improvements.

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No potential conflict of interest was reported by the author.

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