Strontium Is a Potent and Selective Inhibitor of Sensory Irritation

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BACKGROUND. Irritant contact dermatitis occurs following topical exposure to many chemicals found in cosmetics, personal care products, drugs, and during occupational exposure. Signs and symptoms may include sensory irritation (sting, burn, and/or itch), erythema, edema, and vesiculation.

OBJECTIVE. In an attempt to discover new classes of anti-irritant compounds without anesthetic properties, I observed that topical application of strontium salts to intact skin produced potent suppression of sting, burn, and itch caused by many irritant chemicals.

METHODS. Chemically and biologically unrelated irritants were applied with or without strontium salts to the skin of healthy women with self-reported sensitive skin in double-blind, vehicle-controlled, random-treatment assignment trials and sensory irritation was assessed.

RESULTS. Strontium application as a pretreatment or mixed with the irritant substantially suppressed sensory irritation without local anesthetic side-effects.

CONCLUSION. Strontium salts represent a new class of selective inhibitors of sensory irritation and irritant dermatitis.

THE SKIN CONTAINS distinct nerves that convey sensations of touch, vibration, position sense and temperature.[1] Annoying sensations such as stinging, burning, or itching and diffuse pain are transmitted by a subset of unmyelinated, type C nerves called nociceptors that release inflammatory mediators after stimulation by chemical irritants, a process termed "neurogenic inflammation."[2] Many chemicals in topical pharmaceuticals, cosmetics, or which contact the skin during occupational or environmental exposure activate nociceptors and cause irritant dermatitis characterized by rapid-onset stinging, burning, and/or itching which may be accompanied by erythema and edema.[3] The signs and symptoms of irritant dermatitis vary depending on the irritant chemical, its concentration, vehicle, and method of skin exposure.[4,5] For example, low concentrations of lactic or glycolic acid (eg, 5–10%, pH ≈ 2–3) applied to the face usually produce stinging and burning within several minutes after application, without accompanying erythema or edema.[6] By contrast, 70% glycolic acid (pH 0.6) produces stinging and burning that is usually accompanied by erythema and occasionally edema.[7] When the skin is repeatedly exposed to an irritant, the response may become more severe and predispose the skin to a chronic preeczematous condition known as cumulative irritant dermatitis which is responsible for considerable occupational disability.[8]

Conventional local anesthetics like lidocaine effectively block sensory irritation by suppressing nociceptors, but also cause numbness by nonspecifically suppressing other nerves responsible for tactile sensations.[9] Many compounds and plant extracts have been reported to reduce irritation from topical products by reducing the rate of stratum corneum penetration, by altering the vehicle pH, or by chemically reacting with the irritant, but none have demonstrated anti-irritant activity against a broad range of chemically unrelated irritants, especially those with high irritation potential.[10]

Since a safe compound capable of blocking irritant dermatitis would provide considerable benefit, I sought to identify compounds that could effectively block sensory irritant reactions. Simple water soluble strontium salts have proved to be potent and selective inhibitors of chemically induced sensory irritation in humans and do not produce numbness or loss of other tactile sensations.

Materials and Methods

Chemicals and Reagents

The following chemicals were used: strontium nitrate, strontium chloride hexahydrate, and glycolic acid; lactic acid; ethanol; depilatory (4% calcium thioglycolate, pH 12); aluminum chloride (20% in 93% anhydrous ethanol; alumi-

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greater were carried forward as 3 scores and the patches were removed from the subject.

Results

7.5% Lactic Acid (pH 1.9) Sensory Irritation

In a typical time-response curve for lactic acid (7.5%, pH 1.9), the mean irritation score reached 0.5–1.5 within the first minute, with a peak irritation intensity of 2–3 over the next 3–7 minutes, followed by a gradual decline to 1 or less over the 10 minutes (Figure 1). When mixed with lactic acid (7.5%, pH 1.9) at varying concentrations, strontium inhibits sensory irritation in a dose-dependent manner (Table 1). When applied as a pretreatment at varying concentrations 15 minutes prior to lactic acid application, strontium inhibits sensory irritation in a dose-dependent manner (Table 1).

70% Glycolic Acid (pH 0.6) Sensory Irritation

After application of 70% glycolic acid to the forearms of 11 subjects, the mean itching, burning, and stinging peaked 3 minutes after application and decreased minimally over the next 10 minutes (Figure 2). Cumulative sensory irritation was inhibited by 81% ($P < 0.005$). During the study the 11 subjects reported 121 irritation scores. The incidence of each of the four scores of the glycolic acid-treated versus glycolic acid + strontium-treated sides was severe (4): 30 versus 0; moderate (3): 39 versus 8; mild (2): 37 versus 5; slight (1): 6 versus 27; none (0): 9 versus 81.

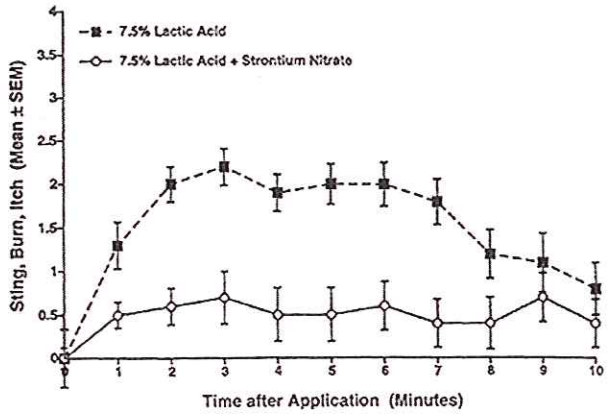

Figure 1. Time course of sensory irritation from 7.5% lactic acid (pH 1.9) ± strontium nitrate. Lactic acid alone (closed squares) or with strontium nitrate (500 mM) was applied to the faces of 10 subjects and sensory irritation was assessed every minute for 10 minutes (see Materials and Methods for scale). Each data point represents the mean ± SEM irritation at each minute for all subjects. Total cumulative irritation (area under the curve) was inhibited by 67% ($P < 0.01$).

Depilatory-Induced Sensory Irritation

Chemical depilatories are basic (pH 9–12) and typically use calcium thioglycolate to dissolve hair keratin.[11] Following control and treatment applications, 23 subjects reported 506 cumulative irritation scores over the course of the entire study. The incidence of each of the four scores of the depilatory versus the depilatory + strontium was severe (4): 0 versus 0; moderate (3): 7 versus 2; mild (2): 45 versus 11; slight (1): 88 versus 53; none (0): 113 versus 187. Cumulative sensory irritation was inhibited by 59% ($P < 0.01$).

Aluminum Chloride-Induced Sensory Irritation

Antiperspirants use aluminum salts alone or in combination with other agents to reduce perspiration. In the moist environment of the axilla, aluminum salts can cause sensory irritation and inflammation.[12] During the study the 16 subjects reported 352 irritation scores. The incidence of each of the four scores of the aluminum chloride versus the aluminum chloride + strontium was severe (4): 12 versus 2; moderate (3): 22 versus 9; mild (2): 30 versus 13; slight (1): 60 versus 41; none (0): 52 versus 111. Cumulative sensory irritation was inhibited by 56% ($P < 0.005$).

Aluminum/Zirconium Salt Erythema

Aluminum/zirconium salt solution (25%) with or without strontium nitrate or chloride was applied to the arms of 29 subjects using occluded patches for 21 days, with erythema evaluated every day. The data in Figure 3 demonstrate that both strontium nitrate (500 mM) and strontium chloride (500 mM) caused nearly complete inhibition of erythema development during the first week and substantially inhibited erythema during the second and third weeks. Total cumulative erythema was reduced by 64% ($P < 0.0001$) with strontium nitrate and by 66% ($P < 0.0001$) with strontium chloride. None of the subjects in any study reported numbness or other abnormal cutaneous sensations on strontium-treated skin.

Discussion

This report demonstrates that strontium salts can effectively suppress sensory irritation caused by structurally and biologically unrelated chemical irritants over a pH range of 0.6–12. Strontium's suppressive activity is not due to the nitrate or chloride anion alone, since sodium nitrate and sodium chloride were inactive (<10% inhibition) at concentrations equimo-

Table 1. Inhibition of Sensory Irritation Scores from 7.5% Lactic Acid (pH 1.9)[a,b]

Strontium Salt (mM)	Strontium Chloride Inhibition		Strontium Nitrate Inhibition		15-Minute Pretreatment with Strontium Nitrate Inhibition	
	% ± SEM	(Subjects, P)	% ± SEM	(Subjects, P)	% ± SEM	(Subjects, P)
500	75 ± 7	(n = 16, <0.005)	68 ± 6	(n = 24, <0.01)	58 ± 12	(n = 16, <0.01)
250	65 ± 12	(n = 17, <0.01)	74 ± 7	(n = 23, <0.01)	48 ± 11	(n = 18, <0.01)
125	64 ± 5	(n = 15, <0.01)	42 ± 14	(n = 15, <0.01)	28 ± 16	(n = 15, <0.01)
63	30 ± 6	(n = 8, <0.01)	34 ± 8	(n = 16, <0.01)	17 ± 10	(n = 18, <0.01)

[a]Strontium nitrate or strontium chloride hexahydrate was either mixed with the lactic acid vehicle (7.5%, pH 1.9, 10% ethanol/water) or preapplied to the face in a 10% ethanol/water vehicle 15 minutes prior to the application of the lactic acid vehicle.
[b]The total cumulative irritation in each study (scores of 1 + 2 + 3 + 4) for the lactic acid-treated side of the face was compared to the lactic acid + strontium-treated side of the face (areas under the curves) and irritation inhibition was calculated as the percent difference.

lar to active concentrations of strontium nitrate (unpublished observations).

Water soluble strontium salts have been reported to directly suppress neuronal depolarization when studied in animals.[13,14] While the mechanism of inhibition is not clear, several processes probably contribute to strontium's inhibitory activity. In aqueous solution, strontium is a divalent ion with an ionic radius similar to the divalent calcium ion (1.13 Å versus 0.99 Å, respectively).[15] Strontium also resembles calcium in its ability to traverse calcium ion channels and trigger neurotransmitter release from nerve endings. In many systems, strontium is, however, less potent than calcium and thus can act as an inhibitor of calcium-dependent depolarization.[14,16–19] Strontium may therefore inhibit calcium-dependent pathways which transduce irritant stimuli into neuronal depolarization. Neurons are also known to be sensitive to compounds which alter the electrostatic field surrounding their plasma membrane and ion channels.[20] Since strontium can alter the electrostatic field of ion channels and reduce ion permeation through them,[21,22] strontium may suppress irritant-induced depolarization of unmyelinated sensory neurons. Strontium salts may also directly act on non-neuronal cells such as keratinocytes or immunoregulatory inflammatory cells. Recent reports demonstrate that strontium salts can suppress keratinocyte-derived tumor necrosis factor-α (TNF-α), interleukin-1α (IL-1α), and IL-6 in in vitro cultures.[23]

The fact that strontium can block irritation as intense as that produced by 70% glycolic acid (pH 0.6) without causing numbness or other changes in cutane-

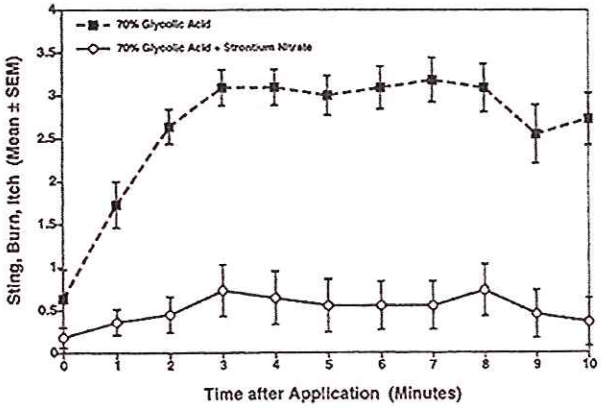

Figure 2. Time course of sensory irritation from unbuffered 70% glycolic acid (pH 0.6) ± strontium nitrate. Glycolic acid only (closed squares) or with strontium nitrate (20%) (open circles) was applied to the same sites on the forearms of 11 subjects. Each data point represents the mean ± SEM irritation at each minute for all subjects. Total cumulative irritation (areas under the curve) was inhibited by 81% ($P < 0.005$).

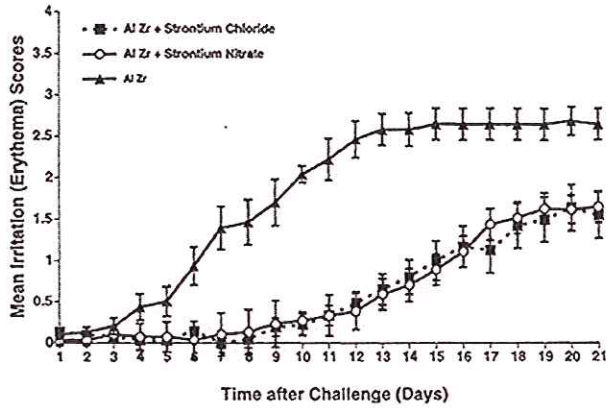

Figure 3. Time course of erythema development induced by aluminum/zirconium salt (25%, pH 3.5) patch application ± strontium salts under occlusion for 21 days. Strontium nitrate (500 mM, open circles) or strontium chloride (500 mM, closed squares) was mixed with the aluminum/zirconium salt solution each day when a new patch was applied. Each data point represents the mean ± SEM for 29 subjects. Total cumulative irritation (areas under the curve) was inhibited by 64% ($P < 0.0001$) for strontium nitrate and 66% for strontium chloride ($P < 0.0001$).

ous sensations, including sensitivity to temperature (Maibach HI, personal communication), suggests that strontium is exquisitely selective in its neuroregulatory activity and probably acts on a subset of sensory neurons. In contrast, local anesthetics such as lidocaine or procaine not only block irritant sensations, but also block tactile sensations, which produces numbness.[9]

I hypothesize that strontium salts act to selectively block the activation of cutaneous type C nociceptors that respond to chemical, thermal, and mechanical stimuli. These polymodal sensory nerves act as primary irritant sensors and respond to noxious stimuli that may cause tissue damage. When activated, nociceptors transmit sensations of itching, burning, stinging, and pain to the brain.[2,24] Upon intense activation, type C nociceptors activate interneurons in the dorsal root ganglion, triggering an antidromic action potential that causes release of substance P, calcitonin gene-related peptide (CGRP), and other chemicals that produce sensory irritation, erythema, and inflammation at the site of stimulation.[3,25] This process, neurogenic inflammation, is believed to be pathogenically important in many irritating and inflammatory conditions, including irritant and allergic contact dermatitis, psoriasis, atopic dermatitis, asthma, rheumatoid arthritis, inflammatory bowel disease and other gastrointestinal disorders.[26] The ability of strontium salts to suppress both sensory irritation and inflammation triggered by a wide range of chemically unrelated irritants is consistent with this hypothesis.

The addition of strontium salts to formulations of topical products can significantly reduce the signs and symptoms of irritant contact dermatitis, which is a significant problem for many people who use cosmetics, personal care products, and topical drugs. Strontium salts represent a new class of selective inhibitors of sensory irritation and irritant contact dermatitis.

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Commentary

The author has demonstrated the mechanism of action of strontium salts in reducing irritancy in a scientific and elegant manner. The importance of this elucidation has most obvious benefit in superficial peeling with glycolic acid, which in the past has been mildly uncomfortable depending on the concentration, pH, and vehicles of the many products available. The predictability of less irritation with 70% products makes the concept most valuable. Worth observing, however, is that the addition of strontium to the acid does not guarantee the absence of untoward irregular penetration of the acid, a phenomenon intrinsic to the compound and making observation of the skin during its use essential. Instead, the sensory phenomena of burning and stinging may be much less prominent, warranting even closer observation in patients who may have irregular penetration, due to excessive defatting of the skin prior to application, for example.

In the demonstration of strontium's efficacy with compounds that are not absorbed such as antiperspirants and depilatories, the author has familarized dermatologists with a group of compounds to identify as irritant-blockers and has further enhanced our expertise in providing comfort for our patients.

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