The Efficacy of Potassium Salts as Agents for Treating Dentin Hypersensitivity

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Formulations containing potassium salts (eg, chloride, nitrate, citrate, oxalate) are widely used for treating dentin hypersensitivity (DH). The purpose of this review was to evaluate evidence for the clinical efficacy of potassium salts in reducing DH and also to consider the biologic basis for any effects. Literature searches were used to identify reports of clinical trials of potassium-containing preparations. Searches revealed 3 trials of potassium nitrate solutions or gels; 2 trials of mouthwashes containing potassium nitrate or citrate; 6 trials of potassium oxalates; and 16 double-blind randomized trials of toothpastes containing potassium nitrate, chloride, or citrate. The toothpaste studies provided quantitative data on treatment effects. These outcome measures were expressed as percentage reductions in sensitivity to cold air and mechanical stimulation and the patients' subjective reports. Trials of topically applied solutions yielded inconsistent results. Potassium-containing mouthwashes produced significant reductions in sensitivity. All potassium-containing toothpastes produced a significant reduction in sensitivity to tactile and air stimuli, as well as subjectively reported sensitivity. In most studies, the active agent (potassium) was superior to the minus-active control (placebo), but a few of the more recent trials have demonstrated significant placebo effects. It is postulated that potassium ions released from toothpastes diffuse along the dentinal tubules to inactivate intradental nerves. However, this principle has never been confirmed in intact human teeth. The mechanism of the desensitizing effects of potassium-containing toothpastes remains uncertain at present.
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Dentin hypersensitivity (DH) is characterized by short, sharp pains that arise typically when thermal, evaporative, mechanical, or osmotic stimuli are applied to exposed dentin, and which cannot be explained by any other form of dental defect or pathology.[1] The majority of "natural" stimuli that cause pain in hypersensitive teeth appear to excite intradental nerves indirectly by increasing fluid flow in dentinal tubules.[2,3] Exceptions to this principle are electric current and thermal stimuli, which can directly activate the smaller-diameter nerve axons in the pulp.[4,5] This hydrodynamic principle prompts 2 basic approaches for treating hypersensitive dentin: *(1)* occlude patent tubules to reduce any stimulus-evoked fluid flow, or *(2)* reduce intradental nerve excitability so that the nerves do not respond to the stimulus-evoked fluid movements. A wide range of agents and procedures have been used to treat dentin hypersensitivity,[6,7] but none are completely effective in every instance. The aims of this

review are *(1)* to evaluate the clinical evidence that potassium salts are effective dentinal desensitizing agents and *(2)* to consider the possible biologic basis for these effects.

Review Procedure

We searched the literature to identify reports of clinical trials of potassium-containing preparations, including toothpastes, mouthwashes, and topical applications. This information has been augmented by material from our own reference libraries. Although most of the information surveyed was taken from full papers in peer-reviewed publications, unrefereed abstracts were also considered if they provided sufficient information about methods and results. The review also covers laboratory-based material that is relevant to understanding the possible biologic mechanisms of the various clinical agents.

Potassium as a Desensitizing Agent

Solutions, Gels, and Mouthrinses

Potassium salts such as caustic potash (potassium hydroxide) were used over 100 years ago as obtundents prior to the introduction of local anesthetics.[8] However, these agents fell out of favor for nearly 100 years. In a largely anecdotal account, Hodosh[9] stated that topical applications of 1 to 15% potassium nitrate (KNO_3), saturated solutions of KNO_3, or a paste containing 10% KNO_3 were effective in reducing dentin hypersensitivity. In a single-blind study, Green et al[10] found that topical applications of a calcium hydroxide paste or a KNO_3 paste (concentrations not specified) gave significantly greater reductions in sensitivity to mechanical and hot stimuli compared with the control (saline). Calcium hydroxide was more effective in reducing pain on cold stimulation. Reinhart et al[11] found that 4 weeks of self-administered daily applications of a 10% KNO_3-glycerin gel were less effective in reducing dentin sensitivity than was a plain glycerin gel.

There is limited information about the efficacy of potassium-containing desensitizing mouthwashes.[12] Gillam et al[13] reported that a 3% KNO_3/silica/sodium fluoride (NaF) mouthrinse caused a significantly greater reduction in DH to mechanical and thermal stimuli than did a silica/NaF control mouthwash. More recently, Yates et al[14] compared the desensitizing efficacy of a compound mouthrinse containing 2% potassium citrate, 0.05% cetylpyridinium chloride, and 0.05% NaF with an identical base formulation lacking these active ingredients. These investigators found that both mouthrinses produced highly significant reductions in tooth sensitivity to tactile and airblast stimulation. However, they failed to detect any significant differences between the desensitizing effectiveness of the test and minus-active or placebo formulations. This latter study is of interest, as it confirmed the strong "placebo response" evident in other recently published clinical trials of desensitizing toothpastes.[15,16]

Potassium Oxalates

Greenhill and Pashley[17] investigated the effects of a variety of desensitizing agents on the hydraulic conductance (permeability) of dentin in vitro. These investigators found that out of 29 agents tested, 30% potassium oxalate solution caused the greatest reduction (98%) in dentin permeability. Since then, the basic dentin disc preparation has been used widely to assess the tubule-blocking ability of potential desensitizing agents in vitro.[18] On the basis of its effectiveness in reducing dentin permeability, potassium oxalates have been used for treating DH. The rationale for the method is that soluble potassium oxalate is converted to insoluble calcium oxalate within dentinal tubules.[17]

In clinical trials, dipotassium oxalate (K_2 oxalate[19]), monopotassium monohydrogen oxalate (KH oxalate[20]), and a combination of the 2[21] have been reported to cause significantly greater reduction in sensitivity than minus-active controls. Gillam et al[22] found that K_2 oxalate (Protect, J. O. Butler) and All Bond 2 resin (Bisco) both reduced DH, but their effects were not significantly different. Cooley and Sandoval[23] and Cuenin et al[24] evaluated the desensitizing efficacy of 3% KH oxalate solutions. These investigators reported that their respective control agents of distilled water and 3% sodium chloride (at pH 2.4) were more effective in reducing sensitivity than KH oxalate. Thus, although in vitro studies suggest that potassium oxalate would be an ideal desensitizing agent, clinical studies have tended to be inconclusive.[22]

Toothpastes

For the purpose of this review, 16 full papers were identified that reported outcomes of clinical trials on toothpastes containing potassium salts (5% KNO_3, 3.75% potassium chloride [KCl], or 5.3%

potassium citrate). The details of the studies are summarized in Table 1. All studies used double-blind, randomized designs. The studies also employed similar exclusion criteria. There were some differences among studies in the inclusion criteria, such as numbers and types of sensitive teeth, the numbers of subjects per group, and the duration of the trial, as well as the modes of sensitivity measurement and the assessment intervals (Table 1). Most included minus-active (placebo) controls (efficacy studies), although a few included only positive controls (equivalence studies). These differences in the trial design made it difficult to attempt quantitative comparisons. However, when analyzed, these studies provided sufficient raw data to enable average percentage changes in sensitivity to be calculated for the active and control formulations. The analysis is confined to the most commonly used and generally accepted sensitivity measures[25]: tactile stimulation (Tables 2 and 3), air-jet stimulation (Table 4), and global subjective evaluations (Table 5).

Several studies have reported that a 5% KNO_3 paste was significantly more effective in reducing sensitivity than a placebo or minus-active control paste.[26–32] Tarbet et al[33] reported that a 5% KNO_3 paste was superior to 3 other desensitizing pastes containing 10% strontium chloride ($SrCl_2$), 2% sodium citrate, or 1.4% formaldehyde. Manochehr-Pour et al,[34] Chesters et al,[35] and West et al[16] reported that whereas pastes containing 5% KNO_3 caused a significant reduction in DH, the performance of this agent was not significantly different from that of the controls ("minus-active" formulation or a paste containing sodium monofluorophosphate [Na MFP]). Some other inconsistencies were identified. Silverman et al[32] and Tarbet et al[33] reported that a 5% KNO_3 paste was superior to a 10% $SrCl_2$ paste. However, in a 12-week semi-quantitative study, Collins et al[27] reported that pastes containing 5% KNO_3 and 10% $SrCl_2$ were comparable in their desensitizing effectiveness. Person et al[36] also showed that toothpastes containing 5% KNO_3 + 0.76% Na MFP and 10% $SrCl_2$ caused a significant increase in the sensitivity thresholds to warm and hot air stimuli after 4 and 8 weeks of use, but the performances of these 2 pastes were not significantly different.

Schiff et al[30] evaluated a combination paste containing 5% KNO_3, 1.3% soluble pyrophosphate, 1.5% copolymer of methoxycellulose and maleic acid, and 0.243% NaF. This paste was significantly more effective than the control paste, which contained all ingredients except the 5% KNO_3. Ayad et al[37] reported that this combination paste was as effective as a standard 5% KNO_3 paste in reducing DH. Schiff et al[31] have reported that a dentifrice containing 5% KNO_3 and 1,500 ppm Na MFP in a precipitated calcium carbonate base was more effective than a control in reducing DH.

Salvato et al[38] reported that a paste containing 3.75% KCl and 0.8% Na MFP was significantly more effective than a control paste lacking both KCl and Na MFP. To counter claims that the desensitizing effects could have been due to the Na MFP in the paste, Silverman et al[39] tested 2 pastes containing 3.75% KCl. One of these contained 0.8% Na MFP. Both of the KCl-containing pastes were shown to be significantly more effective than a control paste that contained all the ingredients of the other pastes, except KCl and Na MFP. Gillam et al[15] compared a KCl/MFP toothpaste and a strontium acetate/NaF toothpaste with a control paste containing Na MFP, calcium glycerophosphate, and NaF. All 3 pastes produced a significant reduction in DH compared to baseline; however, the investigators were unable to demonstrate any significant differences between the 3 formulations.

All studies surveyed have reported that toothpastes containing 5% KNO_3 or 3.75% KCl significantly reduce DH to tactile (Tables 2 and 3) and air-jet (Table 4) stimuli as well as subjective measures (Table 5). In most studies, these pastes are significantly better than the minus-active or placebo controls. However, in 4 studies,[15,16,34,35] both the potassium pastes and the control pastes produced a significant reduction in sensitivity, but there was no significant difference between the performance of the KNO_3 or KCl pastes and the control pastes. Why should the results of these trials be different from the results of the other trials analyzed? Differences in trial outcome could reflect variations in the trial designs.[40] However, the design parameters of these 4 trials[15,16,34,35] lay within the spread of values evident in all the trials analyzed (Table 1). Nor are the differences likely to be due to variations in the initial sensitivity levels, as in all studies analyzed there were no significant differences between the baseline sensitivities of the potassium paste and control groups. It is possible that differences in trial duration could account for variations in the results.[40] The median duration of the 16 trials analyzed was 8 weeks. The studies by Gillam et al[15] and West et al[16] lasted 6 weeks, while the trials of Chesters et al[35] and Manochehr-Pour et al[34] lasted 8 and 12 weeks, respectively. The trial by Chesters et al[35] was the only one to include K citrate as one of the test agents. This trial also employed a novel form

Table 1 Summary of Clinical Trials on Potassium-Containing Toothpastes*

Study	Cells	n (total) completing trial	Test intervals (wk)	Inclusion criteria	Teeth tested	Active agent (formulation†)	Placebo/ control	Sensitivity tests and evaluations
Tarbet et al, 1980[26]	2	27	1,2,3,4	HS teeth	Unknown	5% KNO_3 (1)	Yes	Electrical (threshold), 1-second air jet (0–3 score), subjective (increased or decreased)
Tarbet et al, 1982[33]	4	80	1,2,3,4	≥ 1 HS teeth (probe)	Unknown	5% KNO_3 (1), 10% $SrCl_2$, 2% sodium citrate, 1.4% formaldehyde	No	Electrical (threshold), 1-second air jet (0–3 score), subjective (increased or decreased)
Collins et al, 1984[27]	3	75	2,4,8,12	2+ HS teeth (probe/air)	Unknown	5% KNO_3 (7), 10% $SrCl_2$	Yes	Air blast (0–3 score), mechanical (0–3 score)
Manochehr-Pour et al, 1984[34]	3	75	2,4,8,12	2+ HS teeth (probe/air)	Incisors, canines, premolars	5% KNO_3 (1), 5% KNO_3 (2)	Yes	1-second air jet (0–3 score), mechanical (0–3 score), subjective (0–3 score)
Silverman, 1985[28]	3	68	2,4,8,12	≥ 1 HS teeth	Incisors, canines premolars	5% KNO_3 (1), 5% KNO_3 (2)	Yes	1-second air jet (0–3 score), mechanical (threshold), subjective (0–3 score)
Person et al, 1989[36]	6	119	8	2 HS teeth	Canines, premolars	5% KNO_3 (7), 10% $SrCl_2$, 4 calcium phosphates or hydroxyapatite formulations	No	Hot air (threshold)
Chesters et al, 1992[35]	3	111	3,8	HS teeth (probe/air)	Canines, premolars	5% KNO_3 (7), 5.3% K citrate	Yes (NaMFP)	Electrical (threshold), 1-second air jet (0–3 score), mechanical (threshold)
Salvato et al, 1992[38]	2	41	2,4,8,12	≥ 2 HS teeth (probe/air)	Incisors, canines, premolars	3.75% KCl (3)	Yes	1-second air jet (VAS), mechanical (threshold), subjective (VAS)
Nagata et al, 1994[29]	2	36	2,4,8,12	≥ 1 HS teeth (probe/air)	Unknown	5% KNO_3 (7)	Yes	1-second air jet (0–3 score), mechanical (0–3 score), subjective (0–3 score)
Schiff et al, 1994[30]	2	60	6,12	≥ 2 HS teeth (probe/air)	Incisors, canines, premolars	5% KNO_3 (4)	Yes	1-second air jet (0–3 score), mechanical (threshold), thermal (threshold), subjective (0–3 score)
Ayad et al, 1994[37]	2	87	6,12	≥ 2 HS teeth (probe/air)	Incisors, canines, premolars	5% KNO_3 (4), 5% KNO_3 (2)	No	1-second air jet (0–3 score), mechanical (threshold), subjective (0–3 score)
Silverman et al, 1994[39]	3	62	2,4,8	HS teeth (probe/air)	Incisors, canines, premolars	3.75% KCl (3), 3.75% KCl (7)	Yes	1-second air jet (0–3 score), mechanical (threshold), subjective (0–3 score)
Silverman et al, 1996[32]	4	220	2,4,8	HS teeth (probe/air)	Incisors, canines, premolars, first molars	5% KNO_3 (1), 5% KNO_3 (5), 10% $SrCl_2$	Yes	1-second air jet (VAS), mechanical (threshold), subjective (VAS)
Gillam et al, 1996[15]	3	56	2,6	≥ 2 HS teeth (probe/air)	Incisors, canines, premolars, first molars	3.75% KCl (3), 8% Sr acetate	Yes (NaMFP)	Probe (VAS), 1-second air jet (VAS), subjective (VAS)
West et al, 1997[16]	3	112	2,6‡	≥ 2 HS teeth (probe/air)	Unknown	5% KNO_3 (6), 8% Sr acetate	Yes (NaMFP)	3-second air jet (VAS), mechanical (VAS), subjective (VAS)
Schiff et al, 1998[31]	2	39	4,8	≥ 2 HS teeth (probe/air)	Incisors, canines, premolars	5% KNO_3 (7)	Yes	1-second air jet (0–3 score), mechanical (threshold)

*Commercial products are indicated unless the identity was not included in the publication. All trials used a double-blind and randomized design, with defined exclusion criteria.
†1 = Denquel (Procter & Gamble); 2 = Sensodyne F/Promise (Block Drug Co); 3 = Sensodyne F (Block Drug Co); 4 = Sensitive/Tartar Control (Colgate-Palmolive); 5 = Sensitivity Protection Crest (Procter & Gamble); 6 = Aquafresh Sensitive (SmithKline Beecham); 7 = brand not specified.
‡Plus 4-week "wash-in" period.
HS = hypersensitive; VAS = visual analog scale.

Table 2 Percentage Reduction in Sensitivity to Tactile Stimulus for Potassium-Containing Dentifrices and Controls (Placebo Pastes), Measured by Intensity Scale

Study	Active agent*	Active: reduction from baseline	Placebo: reduction from baseline	Active > placebo (*P* value)
Manochehr-Pour et al, 1984[34]	5% KNO_3 (1)	43%	8%	$P = 0.3$
	5% KNO_3 (2)	47%		$P = 0.21$
Nagata et al, 1994[29]	5% KNO_3 (7)	82%	22%	$P < 0.01$
Gillam et al, 1996[15]	3.75% KCl (3)	48%	46%	$P = 0.49$
West et al, 1997[16]	5% KNO_3 (6)	57%	52%	$P = 0.85$

*1 = Denquel; 2 = Sensodyne F/Promise; 3 = Sensodyne F; 4 = Sensitive/Tartar Control; 5 = Sensitivity Protection Crest; 6 = Aquafresh Sensitive; 7 = brand not specified.

Table 3 Percentage Reduction in Sensitivity to Tactile Stimulus for Potassium-Containing Dentifrices and Controls (Placebo Pastes), Measured as Threshold Force

Study	Active agent*	Active: increase from baseline (= 0%)	Placebo: reduction from baseline (= 0%)	Active > placebo (*P* value)
Silverman, 1985[28]	5% KNO_3 (1)	108%	37%	$P < 0.001$
	5% KNO_3 (2)	130%		$P < 0.001$
Salvato et al, 1992[38]	3.75% KCl (3)	114%	69%	$P = 0.01$
Schiff et al, 1994[30]	5% KNO_3 (4)	145%	22%	$P < 0.001$
Silverman et al, 1994[39]	3.75% KCl (3)	101%	32%	$P < 0.05$
	3.75% KCl (7)	94%		$P < 0.05$
Silverman et al, 1996[32]	5% KNO_3 (1)	99%	68%	$P < 0.001$
	5% KNO_3 (5)	109%		$P < 0.001$
Schiff et al, 1998[31]	5% KNO_3 (7)	254%	110%	$P < 0.0001$

An increase from baseline is a decrease in sensitivity. In this table, baseline is taken as 0%; thus an increase to 100% means a doubling of threshold.
*1 = Denquel; 2 = Sensodyne F/Promise; 3 = Sensodyne F; 4 = Sensitive/Tartar Control; 5 = Sensitivity Protection Crest; 6 = Aquafresh Sensitive; 7 = brand not specified.

Table 4 Percentage Reduction in Sensitivity to Cold Air Stimulus for Potassium-Containing Dentifrices and Controls (Placebo Pastes)

Study	Active agent*	Active: reduction from baseline	Placebo: reduction from baseline	Active > placebo (*P* value)
Tarbet et al, 1980[26]	5% KNO_3 (1)	65%	20%	$P = 0.02$
Manochehr-Pour et al, 1984[34]	5% KNO_3 (1)	63%	37%	$P = 0.38$
	5% KNO_3 (2)	52%		$P = 0.21$
Silverman, 1985[28]	5% KNO_3 (1)	75%	40%	$P < 0.001$
	5% KNO_3 (2)	78%		$P < 0.001$
Salvato et al, 1992[38]	3.75% KCl (3)	66%	32%	$P = 0.001$
Nagata et al, 1994[29]	5% KNO_3 (7)	80%	27%	$P < 0.01$
Schiff et al, 1994[30]	5% KNO_3 (4)	61%	0%	$P < 0.001$
Silverman et al, 1994[39]	3.75% KCl (3)	66%	28%	$P < 0.05$
	3.75% KCl (7)	61%		$P < 0.05$
Silverman et al, 1996[32]	5% KNO_3 (1)	54%	30%	$P < 0.001$
	5% KNO_3 (5)	48%		$P = 0.001$
Gillam et al, 1996[15]	3.75% KCl (3)	51%	48%	$P = 0.52$
West et al, 1997[16]	5% KNO_3 (6)	48%	53%	$P = 0.61$
Schiff et al, 1998[31]	5% KNO_3 (7)	82%	40%	$P < 0.0001$

*1 = Denquel; 2 = Sensodyne F/Promise; 3 = Sensodyne F; 4 = Sensitive/Tartar Control; 5 = Sensitivity Protection Crest; 6 = Aquafresh Sensitive; 7 = brand not specified.

Table 5 Percentage Reduction in Patients' Subjective Ratings of Sensitivity for Potassium-Containing Dentifrices and Controls (Placebo Pastes)

Study	Active agent*	Active: reduction from baseline	Placebo: reduction from baseline	Active > placebo (*P* value)
Tarbet et al, 1980[26]	5% KNO_3 (1)	92%†	21%†	$P = 0.001$
Manochehr-Pour et al, 1984[34]	5% KNO_3 (1)	54%	60%	$P = 0.66$
	5% KNO_3 (2)	36%		$P = 0.81$
Silverman, 1985[28]	5% KNO_3 (1)	71%	36%	$P < 0.001$
	5% KNO_3 (2)	75%		$P < 0.001$
Salvato et al, 1992[38]	3.75% KCl (3)	75%	23%	$P = 0.001$
Nagata et al, 1994[29]	5% KNO_3 (7)	82%	28%	$P < 0.01$
Schiff et al, 1994[30]	5% KNO_3 (4)	52%	30%	$P < 0.01$
Silverman et al, 1994[39]	3.75% KCl (3)	61%	32%	$P < 0.1$
	3.75% KCl (7)	52%		$P < 0.05$
Silverman et al, 1996[32]	5% KNO_3 (1)	55%	29%	$P < 0.001$
	5% KNO_3 (7)	54%		$P = 0.001$
Gillam et al, 1996[15]	3.75% KCl (3)	54%	43%	NS
West et al, 1997[16]	5% KNO_3 (6)	30%	19%	$P = 0.93$

*1 = Denquel; 2 = Sensodyne F/Promise; 3 = Sensodyne F; 4 = Sensitive/Tartar Control; 5 = Sensitivity Protection Crest; 6 = Aquafresh Sensitive; 7 = brand not specified.
†Percentage of subjects with reduced sensitivity.

of analysis (logit analysis: see below). The study by West et al[16] employed a 4-week wash-in period before the trial itself started. Whether these factors could contribute to the outcome differences is not certain. However, the studies that did not demonstrate a significant difference between the KNO_3 or KCl pastes and the control pastes were characterized by an appreciable reduction in sensitivity by the controls, rather than any diminution of the effects of the KNO_3 or KCl pastes (Tables 2 to 5). Thus it seems likely that variations in the extent of the control/placebo responses may account for most of the disparities between trial outcomes.

Effects of Fluoride in a Desensitizing Toothpaste. Fluoride is included in many desensitizing pastes, but its presence is a potentially confounding variable. Topical fluorides are reported to reduce DH.[7] Kanouse and Ash[41] first reported that Na MFP in a toothpaste was an effective desensitizing agent in its own right. West et al[16] confirmed the desensitizing efficacy of a paste containing Na MFP and reported that this "control" paste was no less effective in reducing dentin hypersensitivity than specific desensitizing toothpastes containing 5% KNO_3 or 8% strontium acetate. A similar finding was reported independently by Gillam et al[22] (see above). Several desensitizing toothpastes containing 5.3% K citrate are available, but there is only one published study reporting the desensitizing efficacy of a toothpaste containing 5.3% K citrate.[35] While most other studies report data for sensitivity levels, Chesters et al[35] used a logit analysis. This method does not measure actual sensitivity levels, but assesses efficacy on the basis of the proportions of sensitive and non-sensitive teeth among the study population of all the subjects' canine and premolar teeth at different time-points during the trial. These investigators found that the K citrate paste was significantly more effective than a paste containing 5% KNO_3 and the control paste. All 3 pastes contained 0.8% Na MFP.

Summary: Effects of Potassium Toothpastes. On balance, the majority of trials show that potassium-containing pastes are significantly more effective than controls in reducing DH. Formulations containing KCl and KNO_3 have been accredited by the British Dental Association and the American Dental Association as effective in the treatment of DH (see Tables 2 to 5). However, it is possible that at least some of the desensitizing effects of toothpastes may be due to the actions of constituents other than the designated active agent, eg, abrasive particles.[15,16,42,43] This is supported by in vitro data on the effects of agents on dentin permeability. Pashley et al[44] showed that while the active ingredients of several desensitizing toothpastes produced no significant reduction in dentin permeability when tested on their own, the toothpaste formulations (even when diluted by 1 part in 3) produced significant reductions in dentin permeability. Furthermore, comparable reductions in dentin permeability were produced by "placebo" pastes that lacked the "active" ingredient.

Mode of Action

If potassium-containing preparations are to be regarded as viable desensitizing agents, what is their mode of action? It is difficult to measure directly the effects of desensitizing agents on dentin permeability in human teeth in situ. Thus, the effects of agents on dentin permeability are generally carried out in vitro.

Greenhill and Pashley[17] measured the effects of various desensitizing agents on the permeability (hydraulic conductance) of dentin disc preparations. They found that 30% KNO_3 solution produced no change in dentin permeability. The changes in hydraulic conductance of dentin produced by other potassium salts were: 2 mol/L K carbonate: 8% reduction; 2 mol/L K carbonate + 2% calcium chloride: 26% reduction; 40% zinc chloride + 20% K ferrocyanide: 38% reduction; 30% K oxalate: 98% reduction. The effect of K oxalate was attributed to precipitation of insoluble calcium oxalate within dentinal tubules.[17]

A Direct Action on Intradental Nerves. Since dentin-desensitizing agents such as KNO_3 do not reduce dentin permeability by tubule occlusion,[44] alternative modes of action have to be considered. It has been suggested that potassium ions might exert their desensitizing effects directly on intradental nerves.[45,46] This hypothesis is based on evidence from animal experiments. Concentrated solutions of potassium salts (usually > 135 mmol/L) applied either directly to the pulp or to deep cavities (50 to 100 μm from the pulp) in the teeth of cats or dogs produced a brief excitation of intradental nerves, followed by a period of reduced excitability to stimulation.[47–51] Markowitz et al[50] proposed that the desensitizing effects of potassium ions were due to increased potassium ion concentration ($[K^+]$) in the extracellular fluids surrounding the intradental nerves. The increased $[K^+]$ causes a sustained depolarization of the nerves, resulting in inactivation of action potential generation through a mechanism such as axonal accommodation.[52] There is some evidence that the desensitizing effects of K^+ may vary for different stimuli. Markowitz et al[53] reported that while KCl decreased the responses of intradental nerves to applications of hypertonic NaCl solutions, it was less effective in suppressing responses to stimulation of dentin with air-blasts and mechanical probing. One interpretation of these observations is that there may be different sites or mechanisms of impulse generation for different types of dentinal stimuli.

It is important to emphasize that this mechanism is based on results of experiments on animals and has not been confirmed for human dentin. If the desensitizing effects of potassium are due to action potential inactivation, one might expect a transient pain when a potassium-containing toothpaste is first applied. To our knowledge, this phenomenon has not been reported for toothpastes. However, Green et al,[10] who used near-saturated pastes, noted that: "Upon application of the potassium nitrate, most patients reported discomfort (stinging). No discomfort, or only minor discomfort, was reported on application of the calcium hydroxide."[10p670] Although this pain could have arisen due to a direct action of potassium on intratubular nerves, it could also be due to an osmotic effect exerted by the very concentrated (saturated) solution.[54]

There is no direct evidence that potassium ions exert their desensitizing effects directly on intradental nerves when applied to human dentin. Since it would be very difficult to test this experimentally, it is necessary to use indirect means to examine this hypothesis. It is well established that extracellular $[K^+]$ has a profound effect on the excitability of nerve and muscle cells. Increasing extracellular $[K^+]$ decreases the resting membrane potential (depolarization) of living cells.[55,56] This applies to all cells but will have the greatest consequences for excitable cells (nerve and muscle), which possess voltage-sensitive ion channels. Increasing $[K^+]$ will block the action potential in nerves because the sustained depolarization will leave the voltage-gated Na^+ channels in a state of relative inactivation (in effect, the membrane is held in a prolonged state of refractoriness).

Effect of Potassium Ions on Nerve Excitability. Peacock and Orchardson[57] showed that the amplitudes of the Aβ, Aδ, and C-fiber components of the compound action potentials of isolated nerves were attenuated when extracellular $[K^+]$ was raised to 8 mmol/L and beyond. The conduction block was reversible within 10 minutes of restoring the $[K^+]$ to normal values (4 mmol/L). Although there were no significant differences between the effects of KCl and KNO_3, other experiments indicate that the anion present can have some effect on the K-induced reduction in nerve excitability. It was found that K citrate and K tartrate were more effective in blocking action potential conduction in isolated nerves than K oxalate, which in turn was more effective than KCl or KNO_3.[58] These observations are consistent with the finding that a toothpaste containing 5.3% K citrate was more effective than a 5% KNO_3 paste or a control paste containing Na MFP in reducing numbers of hypersensitive teeth.[35]

Diffusion of Potassium Ions Through Dentin. Potassium ions applied to outer dentin will have to diffuse along the dentinal tubules to achieve (and sustain) a $[K^+]$ of at least 8 mmol/L to inactivate intradental nerves at the pulpal ends of dentinal tubules or even in the peripheral pulp.

It is technically very difficult to measure the $[K^+]$ that might be achieved within dentinal tubules in vivo when concentrated solutions of potassium salts are applied to outer dentin. Therefore, alternative approaches have to be used. Miller et al[59] measured the penetration of K^+ through 800-μm-thick, acid-etched dentin discs in a 2-chamber diffusion cell. The dentin disc separated 2 chambers, which contained phosphate-buffered saline. Potassium nitrate was added to the first chamber to produce an initial $[K^+]$ of 2%. The first chamber was at atmospheric pressure, while the pressure in the second chamber was raised to 20 cm H_2O above atmospheric to mimic the pulpal interstitial fluid pressure. Samples were taken from the second chamber every 60 seconds for 20 minutes and potassium concentrations were measured. Miller et al[59] found very limited potassium diffusion across etched but otherwise untreated discs. However, they found greater amounts of potassium in the second chamber after the dentin discs had received multiple treatments with the Sensitive/Tartar control dentifrice (Colgate-Palmolive). However, the molar concentrations achieved were not stated and could not be calculated from the data presented. Although the discs were soaked overnight in deionized water after being treated with the Sensitive/Tartar control dentifrice, the methodology did not exclude the possibility that the K^+ collected in the second chamber were due to release of K^+ trapped within the tubules of the treated dentin rather than flowing through from the first chamber. This question could be resolved by the use of labeled tracers.

Stead et al[60] used a mathematical model to investigate the factors affecting $[K^+]$ in dentinal tubules. Although only an approximation, the model indicated that the most important factors affecting the steady-state $[K^+]$ in dentinal tubules were the $[K^+]$ in the mouth, the flow velocity of tubular fluid, and the potassium permeability of any functional diffusion barrier between the tubule and the pulp. The model also indicated that under appropriate conditions, applications of high concentrations of potassium ions to outer dentin can increase $[K^+]$ at the inner ends of dentinal tubules to > 10 mmol/L. On the basis of other experiments,[57] such $[K^+]$ would be expected to block action potential propagation in nerves. When K^+ are applied via a toothpaste vehicle, the increase in $[K^+]$ is likely to be transient, and the $[K^+]$ that may be achieved is lessened by conditions that increase the tubular fluid flow velocity or the permeability of the barrier between tubules and the pulp. One interesting finding from the model was that the "steady-state" $[K^+]$ at the inner end of dentinal tubules could vary in the range of 2.6 to 19.2 mmol/L, depending on factors such as the permeability of the tubule-pulp barrier and the velocity of fluid flow outward along the tubules. Tubular $[K^+]$ was lowest when outward fluid flow was high. This raises the intriguing possibility that tubular $[K^+]$ could influence (or even determine) the excitability of intratubular nerves.[61]

This model perhaps oversimplifies a complex problem. Several assumptions have had to be made, based on available information. Figures for average fluid flow through dentinal tubules were based on in vivo measurements made by Vongsavan and Matthews.[62] However, it now seems that fluid flow rates vary considerably among tubules. Macpherson et al[63] used scanning electrochemical microscopy to examine fluid flow through small areas of dentin. These investigators reported that flow was not uniform and that much of the flow can occur through a small number of tubules. If this in vitro situation also applies in vivo, it suggests that there would be limited inward K^+ flux along tubules with high flow rates. But there may be greater inward K^+ flux along adjacent tubules with lower fluid flow rates. This in vitro observation is consistent with morphologic evidence. Dentinal tubules are not simple, parallel, tapered tubes of regular dimensions. The density and diameter of tubules vary at different levels through dentin and at different locations in the tooth.[64] Tubules also exhibit varying degrees of branching,[64] and this may help to explain the regional variations in dentinal fluid flow rates.[63]

Inward diffusion of K^+ along dentinal tubules is opposed by an outward bulk flow of tubular fluid. The diffusion rate varies with the square of the tubule radius, while the fluid flow varies with the fourth power of the tubule radius. This means that halving the tubule diameter will decrease diffusion by 75%, while the fluid flow is reduced by 94%. The consequence is that ionic diffusion is likely to be greater along narrow tubules, as a result of the proportionately greater reduction in bulk fluid flow. This is borne out by experiment. Pashley and Matthews[65] found that diffusion of ^{125}I across dentin disc preparations in the absence of any bulk fluid movement was not significantly affected by removal of a surface smear layer. However, when

inward diffusion was opposed by an outward convective flow generated by a hydrostatic pressure difference of 15 cm H_2O, the reduction in diffusive flux (compared with the no-flow state) was less when the smear layer was present.

In principle, it seems possible to block intradental nerves by raising extracellular [K^+], but the blocking concentrations have to be maintained after application of the desensitizing agent. Evidence from experiments on nerve excitability indicates that potassium-induced effects are transient and reversible.[57] Unless inwardly diffusing K^+ can somehow be trapped at the inner ends of the dentinal tubules, any effects on intratubular nerves will also be transient. However, it must be emphasized that there is no direct evidence that K^+ actually penetrate the dentinal tubules in the manner hypothesized when delivered into the mouth in a toothpaste or other similar vehicle.

Alternative Mechanisms: The Role of the Odontoblast. Recognizing the constraints to K^+ diffusion along the entire length of dentinal tubules, McCormack and Davies[66] proposed an alternative mechanism for K-mediated desensitization. These investigators suggest that K^+ applied to dentin could act through a second messenger system. The hypothesis is that K^+ act on the odontoblast process to release nitric oxide (NO), which in turn produces an analgesic effect by modulating nociceptive input through down-regulation of sensitized nociceptors.[66] Nitric oxide is known to be present in the tooth pulp, where it has diverse functions.[67] For example, it causes vasodilation (hence its former name: endothelium-derived relaxing factor). There is also some evidence that NO that is formed in response to stimulation of pulp nerves may reduce the release of neuropeptides (substance P and calcitonin gene-related peptide [CGRP]) from afferent nerve terminals.[67] Plasma protein extravasation from pulpal blood vessels in response to stimulation of the inferior alveolar nerve is inhibited by a substance P antagonist and a cyclooxygenase inhibitor but is unaffected by the NO synthase (NOS) inhibitor L-NAME (N^{ω}-nitro-L-arginine methyl ester) or by a CGRP antagonist. There is no direct evidence for the mechanism proposed by McCormack and Davies,[66] although odontoblasts do contain enzymes necessary for NO synthesis.[68] However, it is not clear how and where the NO acts, and until more information is obtained, this hypothesis must remain speculative.

Potassium, Odontoblasts, and Sensory Transduction? Perhaps because of their relationship to dentinal tubules and the intradental nerve terminals, the odontoblasts have been implicated in dental pain.[69] However, attempts to provide firm evidence that odontoblasts are actively involved in sensory transduction have so far been unsuccessful. Guo and Davidson[70] used patch-clamping to study isolated odontoblasts and reported that odontoblast membranes contain several types of K^+ and Cl^- channels. These investigators suggest that these channels might play an important role in dentinogenesis and perhaps in sensory transduction. They surmise that stimuli might act (directly or indirectly) on the odontoblast membrane and alter ionic conductances. This could in turn trigger the release of various cytokines, which could evoke or modulate a response from primary afferent terminals. It is of interest to note that cytokines (such as IFN-γ, interleukin-1, tumor necrosis factor α) can stimulate the expression of a calcium-dependent NOS. This sequence of events is consistent with the mechanism hypothesized by McCormack and Davies.[66]

Connections have been described between pulp nerves and cells presumed to be odontoblasts.[71] Gap junctions have been reported between adjacent odontoblasts and between odontoblasts and structures that may be nerve endings. Very recently, Ushiyama et al[72] reported that stimulation of the inferior alveolar nerve causes short-latency (1.2 to 3.5 milliseconds), all-or-none depolarizations of the membrane potential of putative odontoblasts in a lower canine tooth. The depolarizations can follow stimulation frequencies of up to 300 Hz, suggesting that the linkage is not chemically mediated. At present, there is no confirmatory histologic evidence. One must bear in mind that such connections can operate in both directions. The intradental nerves could have a trophic function as well as (or instead of) a sensory function. It is known that there is a decrease in the rate of formation of secondary dentin after denervation with capsaicin.[73]

Conclusion

Although there is evidence that toothpastes containing K^+ are more effective than minus-active preparations in reducing dentinal hypersensitivity, the K-containing preparations are not always superior to controls such as Na MFP. Since solutions of potassium salts (apart from potassium oxalate) do not decrease dentinal permeability, it has been suggested that K^+ diffuse along the dentinal tubules to act on nerve terminals at the pulpal ends of the tubules. Predictions from computer models indicate that K^+ can diffuse along tubules in sufficient amounts to block nerve conduction. However, any

effects will be transient, unless the high intratubular [K^+] can be maintained. At present, there is no convincing evidence that desensitizing preparations based on KCl, KNO_3, and K citrate act in the manner proposed. It is possible that any desensitizing actions of toothpastes may be due to tubule-occluding effects of constituents other than the potassium salts.

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