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REVIEW

Skin Matters: A Review of Topical Treatments for Chronic Pain. Part One: Skin Physiology and Delivery Systems

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ABSTRACT

Chronic pain is a complex disorder with multiple etiologies for which the pathologic mechanisms are still largely unknown, making effective treatment a difficult clinical task. Achieving pain relief along with improved function and quality of life is the primary goal of pain clinicians; however, most patients and healthcare professionals consider 30% pain improvement to be clinically significant—a success level that would be unacceptable in other areas of medicine. Furthermore, patients with chronic pain frequently have multiple comorbidities, including depression and sleep apnea, and most have seen several physicians

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prior to being seen by a pain specialist, have more than three specific pain generators, and are taking multiple medications. The addition of further oral medications to control pain increases the risk of drug–drug interactions and side effects. However, topical analgesics have the advantage of local application with limited systemic levels of drug. Topical therapies benefit from reduced side effects, lower risk of drug–drug interactions, better patient acceptability/compliance, and improved tolerability. This two-part paper is a review of topical analgesics and their potential role in the treatment of chronic pain.

Keywords: Chronic pain; Neuropathic pain; Rational topical polypharmacy; Skin nociception; Topical analgesics

INTRODUCTION

Acute and chronic pain affects millions of Americans. Each year, 25 million people will experience an acute pain event (resolving in <2 weeks), whereas 50 million live with chronic pain [1]; furthermore, as the American population ages, the incidence of chronic pain is expected to only increase. For instance, up to 10% of all American adults report chronic pain; however, this increases to 60% in those older than 65 [2]. Missed work and increased healthcare costs attributed to chronic pain conditions have been estimated to exceed 100 billion dollars annually [3]. Chronic pain manifests with both behavioral and physical components, and it is known that genetics, environment, and diet all impact the generation of pain and analgesic responsiveness. Most often, the clinical presentation and treatment of chronic pain patients is extremely complex, and simple

solutions or single modalilty therapy offer limited benefit. Nevertheless, a general lack of acceptance of this axiom may explain why current chronic pain treatments are not more efficacious. Clearly, there is a tremendous need to better understand chronic pain mechanisms and to create novel and effective multimodal treatment options for clinicians and patients.

Topical analgesics (TAs) have been used for centuries in the traditional medical approaches of China and other countries. For example, writings from before 600 BC on the treatment of headache list a plethora of topical options, including botanicals and animal-derived products [4]. The first formal report of the pain-reducing properties of topical capsaicin in the West appeared in 1850 as a recommendation to use an alcoholic hot pepper extract for burning or itching extremities [5]. Unfortunately, despite the long history of TA use, their well-documented benefits, and their current use in traditional types of medicine, TAs are underutilized.

Neuropathic pain is a chronic condition of the somatosensory nervous system that severely impairs the health and quality of life of 5–10% of humans, with a total United States economic impact estimated at more than $600 billion annually [6]. Neuropathic pain, by definition, originates from neural pathology and dysfunctions in the peripheral and/or central nervous system (CNS) resulting in high levels of cortical activity among regions known to influence pain perception. Many types of neuropathic pain originate within peripheral tissues, such as skin, ostensibly driven by hyperexcitability of primary afferents. As such, topical approaches may be effective in alleviating neuropathic pain at the source, and this concept underlies most of the evidence for the function of TAs. TAs can target regional pain through affected skin, where they interfere with

the peripheral nociceptive mechanisms directly, by modulating the activity of small nerve fibers, and/or indirectly, via non-neuron interactions (e.g., skin resident cells, keratinocytes, and monocyte-derived infiltrated immune cells). In addition, TAs may reach deeper tissues and act on underlying somatic peripheral nerves.

TAs can be delivered as liquids, ointments, gels, powders, creams, semisolids, emulsions, patches, foams, or aerosols. They are mixed with adjuvants, which enhance viscosity and permeation, and emollients and preservatives. Effective TAs are water soluble and lipophilic, with the delivery goals of reducing drug concentration, increasing local tissue absorption, and holding the drug at the application site. Moreover, TAs avoid standard issues that follow the oral ingestion of medications, such as gastric ulceration, first-pass hepatic metabolism, and problems associated with variable serum concentrations. However, there is distinct individual variation in both skin physiology and metabolism that might affect the absorption and drug distribution of TAs. Ultrasound, electricity, and lasers have all been used to facilitate the permeability and delivery of various topical preparations [7, 8]. This article will not discuss either these delivery approaches or the use of TAs for venipuncture in pediatrics. In this first part of this two-part article on TAs, we discuss basic skin innervation and immunocytochemical characteristics under both normal and neuropathic conditions. Insights into skin function and potential therapies are derived from a discussion of research models using topical capsaicin. We also review other pharmacologic formulations and delivery systems.

This review article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

MORPHOLOGY, INNERVATION, AND IMMUNOCYTOCHEMICAL CHARACTERISTICS OF SKIN

The skin is a protective barrier designed to absorb daily physical abuse and environmental extremes. Skin is also the largest sensory organ, providing an essential interface between an organism and external stimuli. However, its exposed location and extreme complexity predisposes the skin, and its innervation, to hundreds of chronic afflictions, many of which are associated with chronic pain and lack effective, safe therapeutic options, including postherpetic neuralgia (PHN), diabetic peripheral polyneuropathy (DPPN), and complex regional pain syndrome (CRPS). In addition, the skin and its innervation are especially vulnerable to pharmacotoxic side effects. It is a highly heterogenous organ that integrates elements of integumentary, nervous, vascular, immune, and endocrine functions as well as self-renewing mechanisms. This complexity provides a wide variety of important functions including physical protection, immunologic defense, extremely sensitive multimodal stimulus detection, thermoregulation, hormonal regulation, pliability, and physical appeal. As such the composition of the skin and the varieties of innervation vary dependent upon different functional demands needed over different parts of the body surface.

A major challenge to the development of more effective therapeutic strategies for treating neuropathic pain originating from the skin and its innervation is to identify the nature of the underlying pathologies and how they may differ across diseases and patients. Multimolecular assessments of skin biopsies are revealing previously unknown pathologies that

Table 1 Skin receptors related to pain perception in humans

ASIC3
PAR2
P2X3
TRAAK
TREK1/2
TRPA1
TRPM8
TRPV1
VR1

List is not exhaustive. Based on: Dubin AE, Patapoutian A. Nociceptors: the sensors of the pain pathway. J Clin Invest. 2010;120:3760–3772 and Gold MS, Gebhart GF. Nociceptor sensitization in pain pathogenesis. Nat Med. 2010;16:1248–1257

provide valuable insight into the particular symptoms of individual patients and the most appropriate strategies for treatment. Analyses of skin punch biopsies provide a method for detecting potential pathologies that may provide insight into chronic pain mechanisms and potential therapeutic targets [9–15]. Immunocytochemical analyses of axons and endings has become more selective and reliable as well as increasingly viable for exploring complex pain mechanisms and validating human tissue targets [16–19]. Various receptors are involved in cutaneous nociception, a variety of which are listed in Table 1.

The Paradoxical Loss of Epidermal Endings

Until the late 1980s, it was widely believed that the epidermis contained few sensory endings, and that most of the small-caliber innervation implicated in cutaneous sensations of pain (i.e., nociceptors) was located in the dermis. However, the development of an antibody against the enzyme ubiquitin C-terminal hydrolase 1 (UCHL-1, also called protein gene product 9.5 [PGP9.5]), which is enriched in neuroendocrine cells, revealed extensive, previously unknown innervation, with the epidermis being a primary site of small-fiber nociceptor endings (Fig. 1a, d) [17, 20–23]. Paradoxically, however, PGP9.5 immunolabeling of punch biopsies from several types of intractable chronic pain afflictions revealed a significant depletion of this intraepidermal nociceptor innervation in these neuropathic pain states (Fig. 1d) [9–15, 18, 19, 24]. Two hypotheses to explain this apparent paradox are: (1) the deafferentation hypothesis, which proposes that CNS neurons may be sensitized by loss of input; and (2) the irritable nociceptors hypothesis, which proposes that the remaining innervation may be hyperactive [25]. Several lines of evidence have revealed that the remaining sensory innervation is, indeed, hyperactive; however, the source of the hyperactivity has yet to be established [26–32]. One potential source may be the selective loss of some innervation types which normally have a regulatory impact, whereas another source is likely to be that the remaining innervation has increased branching and changes in neurochemistry (Fig. 1d)—for example, upregulation of the transient receptor potential cation channel, subfamily V, member 1 (TRPV1) [17–19]. However, such changes have yet to be systematically explored. Although the density of epidermal innervation is generally lower in painful skin, a substantial depletion of innervation can also occur without pain following a herpes zoster outbreak or due to normal aging [33].
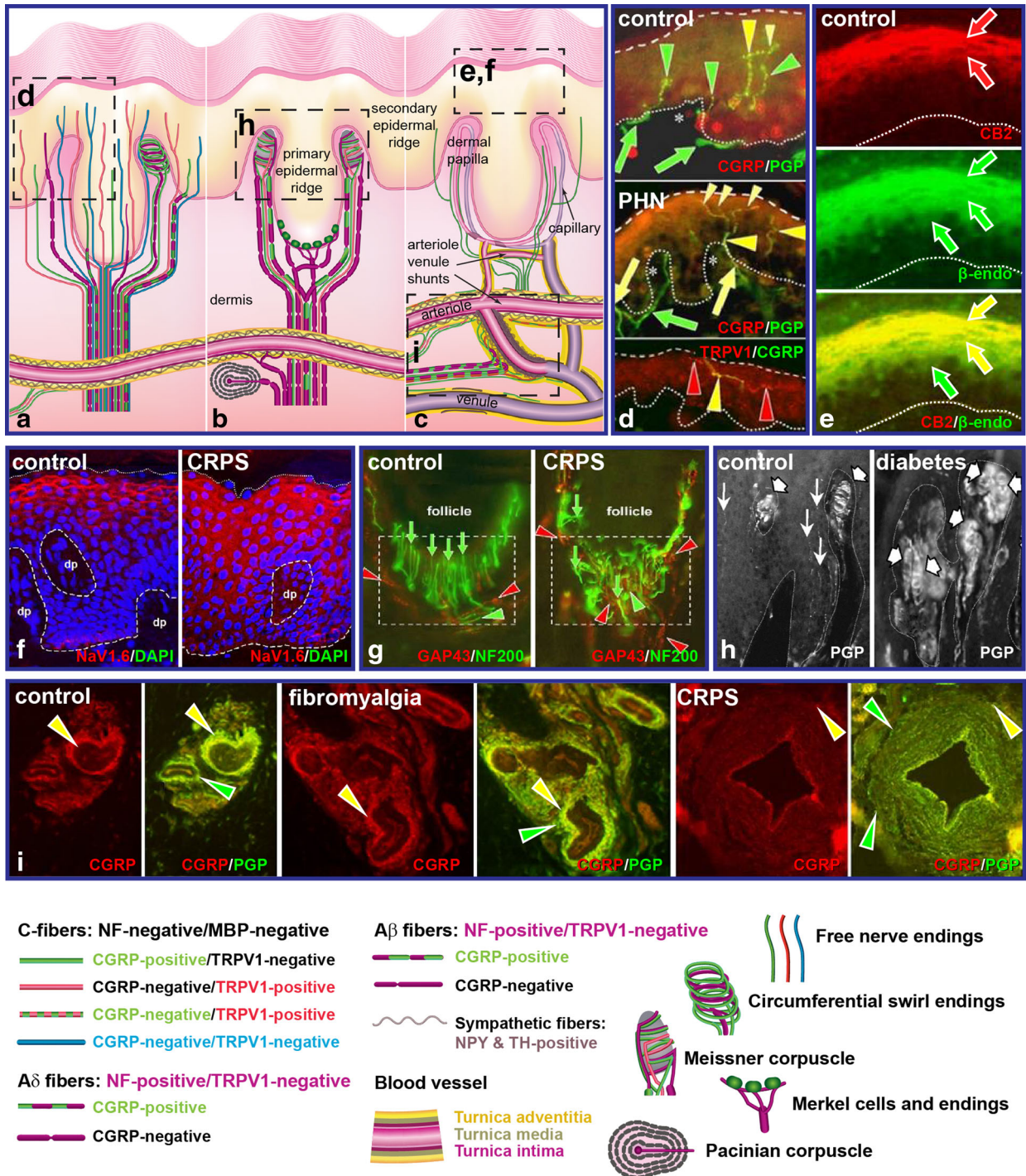
Pathologies of Epidermal Keratinocyte Neural Chemistry

A contributing factor to the hyperactivity of epidermal innervation may be pathologies involving the signaling of epidermal keratinocytes. Although keratinocytes are typically regarded as nonexcitable cells, they express numerous neurospecific signaling molecules; however, the function of these molecules is typically viewed in the context of keratinocyte proliferation and differentiation. Substantial recent evidence indicates that keratinocytes have both algesic and analgesic properties that are involved in sensory transduction and the modulation of activity at epidermal sensory endings. For example, analgesic mechanisms involve the expression of β-endorphin among the keratinocytes of the upper stratum which can be released by activation of the endothelin-1 receptor B (ETB) and the cannabinoid 2 receptor (CB2), which are coexpressed in the same keratinocytes of the upper stratum (Fig. 1e). The release of β-endorphin, in turn, may suppress the activity of epidermal endings that express μ-opioid receptors, G-protein-activated inward-rectifying potassium channels (GIRK), and the proinflammatory neuropeptides calcitonin gene-related peptide (CGRP) and substance P (SP) [34, 35]. The algesic mechanisms involve the keratinocyte production of ATP and the β-isoform of CGRP, which may be released through the activation of voltage-gated sodium channels (NaV) expressed on the keratinocytes (Fig. 1f) [36, 37]. The release of ATP may activate purinergic receptors (e.g., P2X3), which are expressed primarily on epidermal endings that lack CGRP and SP [38]. Recent evidence indicates that the neurochemistry of keratinocytes obtained from the painful skin of patients with PHN and CRPS is skewed toward an over-representation of algesic components (Fig. 1f) and an underrepresentation of analgesic components.

Pathologies among Aβ Fibers

The Aβ cutaneous innervation is generally regarded as mediating low-threshold mechanoreceptive sensations, with implications that it may play an inhibitory role in pain modulation as hypothesized by the gate theory. Currently, this innervation type has received little attention in biopsy assessments of skin associated with chronic pain conditions, primarily due to the fact that this innervation is concentrated in the glabrous and hairy skin of the hands and feet, which are rarely biopsied. However, multimolecular labeling of glabrous and hairy skin, primarily in rodents and monkeys and a few cases in humans, have revealed that individual Meissner corpuscles and piloneural complexes normally have a complex highly ordered morphology consisting of endings from multiple Aβ fibers with an intermingling of several types of C-fibers (Fig. 1b, g) [22, 39–41]. Moreover, both the Aβ and C fiber endings normally express immunochemically detected properties typically associated with nociceptors. These features indicate that the Meissner corpuscles and the piloneural complexes are sites of sensory integration that may have nociceptive involvement. Another paradox of chronic pain conditions is the common complaint that the painful sites also manifest numbness, which has been attributed to a likely loss of Aβ fiber innervation. However, assessments of extensive skin samples of rhesus monkeys that have naturally occurring type 2 diabetes and a few humans with unmanageable CRPS that required limb amputation revealed that Meissner corpuscles and piloneural complexes

a dermis

b secondary epidermal ridge / primary epidermal ridge / dermis

c dermal papilla / arteriole venule shunts / capillary / arteriole / venule

d control — CGRP/PGP / PHN — CGRP/PGP / TRPV1/CGRP

e control — CB2 / β-endo / CB2/β-endo

f control / CRPS — dp — NaV1.6/DAPI

g control — follicle / CRPS — follicle — GAP43/NF200

h control / diabetes — PGP

i control — CGRP — CGRP/PGP / fibromyalgia — CGRP — CGRP/PGP / CRPS — CGRP — CGRP/PGP

C-fibers: NF-negative/MBP-negative
- CGRP-positive/TRPV1-negative
- CGRP-negative/TRPV1-positive
- CGRP-negative/TRPV1-positive
- CGRP-negative/TRPV1-negative

Aδ fibers: NF-positive/TRPV1-negative
- CGRP-positive
- CGRP-negative

Aβ fibers: NF-positive/TRPV1-negative
- CGRP-positive
- CGRP-negative

Sympathetic fibers: NPY & TH-positive

Blood vessel
- Turnica adventitia
- Turnica media
- Turnica intima

Free nerve endings

Circumferential swirl endings

Meissner corpuscle

Merkel cells and endings

Pacinian corpuscle

were present, but were profoundly disorganized (Fig. 1g, h) [17, 18]. These data suggest that the numbness might be due to abnormal activity from this innervation rather than a loss of innervation, and aberrant piloneural complexes observed in the patients with CRPS may contribute to the profound mechanical allodynia caused by slight movements of hairs.

◄ **Fig. 1** Selected examples of chronic pain-related pathologies detected by multimolecular immunofluorescence assessments of skin biopsies from humans and rhesus monkeys. **a–c** Schematic illustration of all the types of innervation in normal glabrous fingertip based on a compilation from several studies (from [41]). **a** C-fiber and Aδ-fiber innervation of the epidermis and arterioles. **b** Aβ-fiber innervation. **c** Vascular innervation. *Broken-line boxes* indicate locations where immunolabelled images are shown in corresponding **d–i**. **d** Changes in the immunochemical characteristics in patients with postherpetic neuralgia (from [19]). **e** Expression of cannabinoid receptor 2 and β-endorphin in normal epidermal keratinocytes, which are part of an analgesic regulatory mechanism (from [34]). **f** Expression of $Na_V1.6$ on epidermal keratinocytes, which is increased in patients with CRPS type 1 as part of an increased algesic mechanism (from [36]). **g** Disarray of Aβ-fiber lanceolate endings around hair follicles of patients with CRPS type 1 (from [18]). **h** Excess disorganized Aβ-fiber Meissner corpuscles in the dermal papillae of rhesus monkeys with type 2 diabetic neuropathy (from [17]). **i** Excess innervation of arteriole venule shunts of patients with fibromyalgia (from [46]), and loss of arteriole innervation coupled with hypertrophy of the tunica media in patients with CRPS type 1 [5]. *CGRP* calcitonin gene-related peptide, *CPRS* chronic regional pain syndrome, *MBP* maltose binding protein, *NPY* neuropeptide Y, *TH*, tyrosine hydroxylase (positive nerve terminals)

Pathologies among Vascular Innervation

Afferents containing CGRP/SP have been implicated in an axon-reflex-mediated increase in vascular dilation and permeability of capillaries and precapillary arterioles in the upper dermis as well as in pain sensation in response to intense heat. However, relatively little research has been directed toward the extensive, dense, sensory innervation to the arterioles and arteriole–venule shunts (AVS) in the deeper dermis [16, 40, 41]. Nearly all of the attention to the innervation of these deeper vessels has been focused on the sympathetic innervation, which is primarily noradrenergic, with a recently identified cholinergic contingent [16]. The sensory innervation of deeper vessels consists of several types of C and Aδ fibers, most of which also express CGRP and SP (Fig. 1c, i) [16, 40, 42–45]. This innervation is presumably involved in monitoring vascular dynamics and likely plays a vasodilatory effector role to counter sympathetically mediated vasoconstriction [44]. However, recent evidence indicates that these arteriole and AVS afferents may also contribute to conscious tactile perceptions, including pain [16]. The convergence of the sensory and sympathetic innervation among cutaneous vasculature may be a specific site of sudomotor disorders and sympathetic involvement in chronic pain conditions such as CRPS and fibromyalgia, where profound pathologies of this innervation have been observed in the skin (Fig. 1i) [18, 46].

CLINICAL PHASE STUDIES OF HUMAN EXPERIMENTAL PAIN

Capsaicin, 8-methyl-N-vanillyl-6-nonenamide, is the active ingredient in chili peppers which provokes a burning sensation by binding to a heat-activated calcium channel, TRPV1. These channels normally open between 37 and 45 °C, but, when bound, the threshold decreases to less than 37 °C or the physiologic body temperature [47]. This stimulates the exocytosis of SP, leading to mast cell degranulation of histamine and serotonin release from platelets. A flare and weal response occurs rapidly while a poorly localized, protracted dull pain lingers from slow-conducting C nerve fibers. Mechanical and heat hyperalgesia ensue as pain thresholds decrease for central and peripheral nociceptors. An area of mechanical allodynia and secondary hyperalgesia occurs due to the activation of adjacent dermatomes. When capsaicin is given
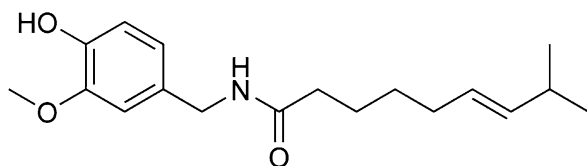
Fig. 2 Capsaicin

intradermally, acute pain is elicited by the activation of fast A fibers and as a direct effect of capsaicin. Elements of chronic neuropathic pain such as mechanothermal hyperalgesia and allodynia are mediated through activation of C fibers. These pain pathways are naturally activated by tissue abrasions, burns, and incisions. The chemical structure of capsaicin is shown in Fig. 2.

There are two capsaicin research models—the intradermal capsaicin and the heat/capsaicin sensitization model. Both models have been well validated as reliable means of producing painful stimuli that include acute sharp pain, burning sensation, mechanical and heat hyperalgesia, and tactile allodynia. Intradermal capsaicin-induced pain is dose dependent, with a minimum dose requirement of 10 μg to elicit a measurable response and ≥100 μg for a robust reaction [48]. Both models have been extensively studied with different classes of pain medications that include opioids, N-methyl-D-aspartic acid (NMDA) antagonists, cannabinoids, sodium and/or calcium channel antagonists, tricyclic antidepressants (TCAs), and cyclooxygenase inhibitors. The pharmacology of the two models appears to be similar. Opioids, cannabinoids, and NMDA antagonists significantly decrease pain and allodynia in this human model. Other nonopioid analgesics (intravenous lidocaine, TCAs, and nonsteroidal anti-inflammatory drugs [NSAIDs]) have minimal effect. Gabapentin, a calcium channel modulator, has

shown equivocal results under this model, but its analog, pregabalin, decreased capsaicin-induced pain and hyperalgesia [49]. However, if one looks closely at the studies, the differences appear attributable to the different drug doses and dose scheduling [50–52]. Table 2 shows properties of different classes of topical drugs studied using capsaicin models.

A sodium channel antagonist (4030W92) was shown to be ineffective in an intradermal capsaicin model and had negative effect in a multicenter trial on neuropathic pain with mappable allodynia [53, 54]. Cannabis was studied in this model, but the results showed that a low dose was no different from placebo, and a medium dose reduced, whereas a high dose increased, pain [55].

The identification of the nature of the underlying pathologies and how they may differ from disease to disease and patient to patient pose a major challenge to the development of more effective strategies and therapeutics for treating neuropathic pain originating from the skin and its innervation. Multimolecular assessments of skin biopsies are just beginning to reveal previously unknown pathologies that may provide valuable insight into the particular symptoms of individual patients and the most appropriate strategies for their treatment. The density of epidermal innervation has received major emphasis in using skin biopsies as an analytical and diagnostic tool for neuropathic pain. However, these same skin biopsies also provide insight into other potential contributors and therapeutic targets for chronic pain such as pathologies among neurochemical properties of epidermal keratinocytes, perturbed Aβ fiber innervation, and aberrations among the converging sensory and sympathetic innervation on arterioles and AVS.

Table 2 Studies of topical compounds using capsaicin models

Compound class	Drug	Route	Dose	Experimental pain effect	Neuropathic pain effect	Postoperative pain effect	Reference(s)
Opioid	Alfentanil	IV	75 ng/mL	Positive	Positive as a class	Positive as a class	[50, 51, 61–64]
	Remifentanil	IV	0.1 µg/kg/min	Positive			
	Hydromorphone	PO	8 mg	Positive			
	Morphine	PO	30 mg	Positive			
	Morphine	IV	10 mg	Positive			
	Alfentanil	IV	50 ng/mL	Negative			
	Alfentanil	IV	200 ng/mL	Positive			
NMDA antagonist	Ketamine	IV	150 ng/mL	Positive	Disappointing as a class	Positive only in combination with an opioid	[49, 50, 52, 61]
	Dextromethorphan	PO	30 mg	Negative			
	Ketamine	IV	0.1 mg/kg then 7 µg/kg/min	Positive			
	Magnesium	IV	0.2 mmol/kg then 0.2 mmol/kg/min for 90 min	Negative			
Alpha 2 agonist	Clonidine	Intrathecal	150 µg	Positive	Positive	Positive only in combination with an opioid	[65]
	Clonidine	IV	150 µg	Negative			

Table 2 continued

Compound class	Drug	Route	Dose	Experimental pain effect	Neuropathic pain effect	Postoperative pain effect	Reference(s)
Alpha 2 delta ligand	Gabapentin	PO	1,200 mg	Positive	Positive as a class	Positive only in combination with an opioid	[49–52, 66–69]
	Gabapentin	PO	2,400 mg/day	Positive			
	Gabapentin	PO	1,800 mg/day	Negative			[61, 65]
	Pregabalin	PO	300 mg	Positive			
Antihistamine	Diphenhydramine	PO	50 mg	Negative	Negative	Negative	[49]
	Diphenhydramine	IV	25 mg	Negative			[61, 65]
Tricyclic antidepressant	Desipramine	PO	225 mg/day	Negative	Positive	Negative	[65–67]
	Amitriptyline	IM	25 mg	Negative			
GABA-A agonist	Midazolam	IM	4 mg	Negative	Negative as a class	Negative as a class	[65]
Na-channel block	Lidocaine	IV	3 µg/mL	Negative	Disappointing as a class	Disappointing as a class	[65]
	Lidocaine	IV	2 mg/kg then 3 µg/kg/h	Positive (but limited)			[68]
	Lidocaine	IV	5 mg/kg over 50 min	Positive			[69]
	Mexiletine	PO	859 mg/day	Positive (but limited)			[70]
	Lamotrigine	PO	300 mg	Negative			[53]
	Lamotrigine	PO	400 mg	Negative			[63]
Adenosine agonist	Adenosine	IV	65 µg/kg/min for 85 min	Negative	Negative	Positive (spinal)	[72]

Table 2 continued

Compound class	Drug	Route	Dose	Experimental pain effect	Neuropathic pain effect	Postoperative pain effect	Reference(s)
Cannabinoids	Cannabis	Inhaled	3 doses (2%, 4%, 6%)	Positive 4%, negative 2 % and 6%	Positive 6%, negative 2 and 4%	Modest benefit	[55]
	Cannabis	Inhaled	4%	Positive	Positive (low dose)		[73]
	THC/Cannabidiol	Inhaled	3.56% THC	Equivocal	Negative (high dose) (sativex)		
TRPV1 antagonist	REN-1654	PO	Oral 100 mg	Negative	Negative	N/a[a]	[74]
AMPA antagonist	NGX426	PO	10 mg/cc	Positive	N/a[b]	N/a[b]	[75]
Magnesium	Magnesium	IV	0.2 mmol/kg^{-1}	Negative	N/a[b]	N/a[b]	[76]

AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, *GABA* γ-aminobutyric acid, *IM* intramuscularly, *IV* intravenously, *NMDA* *N*-methyl-D-aspartic acid, *PO* orally, *THC* tetrahydrocannabinol, *TRPV1* transient receptor potential cation channel, subfamily V, member 1

[a] The patients in this study had a neuropathic component to their pain, but not post-surgical

[b] This study was done in healthy subjects without neuropathic or postoperative pain

FORMULATIONS AND APPLICATIONS

When considering the use of a TA, the risk and severity of adverse effects and drug–drug interactions are less than for the same analgesic administered systemically [56]. Obviously, this is clinically relevant when managing a patient who has been prescribed multiple concurrent systemic medications. Recent guidelines regarding the pharmacologic management of pain in older adults emphasize this point [57]. Furthermore, as TAs typically do not involve dose titration, whereas many systemic agents do, this may provide an additional benefit. Choosing which TA to use depends upon the clinical setting in which the medication is being used. For example, application of the 5% lidocaine patch, by protecting allodynic skin from being stimulated, may reduce allodynia in PHN [58].

Recently, three topical NSAIDs and the capsaicin 8% patch (C8P) have been approved by the Food and Drug Administration. Topical preparations containing opioids, local anesthetics (LAs), antidepressants, glutamate receptor antagonists, α-adrenergic receptor agonists, adenosine, cannabinoids, cholinergic receptor agonists, gabapentinoids, prostanoids, bradykinin, ATP, biogenic amines, and nerve growth factor are each at various developmental stages [59]. Considering using TAs that have more than one mechanism of action might be more efficacious than use of a single TA; for example, the antinociceptive effects of topical morphine may be enhanced by a topical cannabinoid as suggested in a rat study [60]. This is intuitive for those who treat chronic pain and could be considered "rational topical polypharmacy".

CONCLUSION

TAs provide a therapeutic option with decreased side effects and decreased drug–drug interactions for patients with neuropathic and other disabling chronic pain syndromes. The range of potential targets that can be used as TAs is expanding. The pharmaceutical industry is taking interest in developing some of these options into marketable products, all of which should help patients with pain. In Part Two of this article, we discuss specific drugs that can be used as TAs as well as the potential to determine through physical examination who would benefit most from specific agents.

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Compliance with ethics guidelines. This review article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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