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The Pivotal Role of Transient Receptor Potential (TRP) Ion Channels in the Pathogenesis of Sensitive Skin

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Abstract

Sensitive skin syndrome is a challenging and important condition in the domain of disease management and also in skin care products and cosmetic manufacturing. Conditions like Psoriasis, Rosacea, Contact and Atopic Dermatitis are associated with it. The perception of itch is translated to our brain by neuronal depolarization signals initiated by aberrant Transient Receptor Potential (TRV) Channels; mainly TRPV1, TRPV3, TRPV4 and TRPA1 through a complex inflammatory cascades and mediators. The discovery of these mediators and pathways not only broaden our understanding of the skin-nervous system interaction during the body innate response to adversity but also may provide therapeutic solution to a number of diseases which share similar pathogenesis and aetiology.

Keywords: Dermatology; Central nervous system; keratinocytes

Introduction

Sensitive skin syndrome

Sensitive skin is defined as being a subjective symptom with abnormal sensations in response to a variety of factors [1]. Sensitive Skin Syndrome (SSS) is a widely documented skin condition with significant and sometimes exaggerated to subject of complaints by the affected individual with the following sensations such as itching, tingling, burning, stinging, pain and a feeling of skin tightness when exposed to cosmeceuticals products like cleansers, moisturizers and sunscreens often in an exaggerated extreme environmental condition like hot and cold weathers. Some chronic skin conditions like Rosacea, Psoriasis, Allergic Contact Dermatitis and Atopic Dermatitis are found difficult to treat, hence this may predispose and related to SSS [2,3].

Quite often SSS may be dismissed as psychogenic, somatization or even hysteria; no obvious sign appeared on examination of the face of the sufferers. The skin may look normal on sensitive skin. With advances in epidemiology, molecular biology, dermatology together with neuronal research, data suggested that SSS has an organic pathology. SSS is reported for all types skin and different ethnicity [4]. Female patients with fair skin type with age ranging from thirty to forty years old are mostly prone to SSS and the number of patient life that has been affected by SSS have also be reported [5]. SSS does not only affect the face, but scalp, genitalia, and even hands [2,6]. Patients may need to take sick leave and off time from work because of the swellings, redness and the unpleasant sensation of itch and pain [7,8]. Thus, the burden of the disease on the population is significant. The prevalence may be escalating in the modern affluent societies; both in the west and east; where there is a preponderance use of cosmeceuticals. Recent molecular research gives the evidence that SSS was a disease in the Skin – Afferent neurones – Central Nervous System (CNS) comprising the Dorsal Root Ganglion (DRG), Spinothalamic tract, Thalamus and Cerebral cortex through TRP Channels and its moieties [9].

TRP Channels

TRP channels are widely distributed and readily found in the animal kingdom consisting of both the invertebrate and vertebrate including mammals. Till now, 28 different TRP channels grouped under six families: TRPV (vanilloid), TRPA (ankyrin), TRPM (melastatin), TRPC (canonical), TRPML (mucolipin), TRPP (polycystin) are identified [10-12]. Many tissues, besides the nervous systems, have been shown to possess TRP channel and receptors. **Table 1** showed the TRP channels anatomical distribution, functions, and proposed role in mediating sensations in sensitive skins. Elucidation of TRP

neuronal connections and networks enable us to better understand the normal or diseased state of the body.

Table 1. Anatomical distribution, functions, and proposed role of some of the TRP channels.

	Distribution	Presence in Affluence Sensory Neurones	Direct Sensory Processing	Epidermal Homeostasis and Barrier Function	Epidermal Differentiation Proliferation	Neurogenic inflammation Immune response	Mode of action
TRPV 1	Keratinocytes Nociceptive sensory neurones Fibroblasts Mast cells Endothelial cells Langerhans Cells Sebocytes	+	+	+	+	+Il1 IL8 PEG2 TGFb2 MMP1 UV	Calcium influx
TRPV 3	Highly expressed in keratinocytes	-	-	+	+	+Trpv3gly57ser mutation Atopic dermatitis itch	Calcium influx
TRPV 4	Keratinocytes Neurones	+	+	+	+	+	Calcium influx
TRPA 1	Abundantly located in nociceptive sensory neurones, central terminus in the spinal cord, dorsal horn Mast cells Keratinocytes	+	+	+	+	+	Calcium influx
TRPM 8	Melanocytes Sensory neurones	+	+	+	+	+	Calcium influx

'+' denotes positive involvement; '-' denotes no involvement

TRP receptors can directly mediate neuronal signals through depolarization along afferent neurones to CNS which result to the perception of itch, pain, tingling, and burning. The depolarization involves calcium ion influx to the neuronal cell. This is referred to the Direct Neurogenic Transmission which mainly involved TRPV1, TRPA1 and TRPV4. These pruritogenic neurones are supposed to be directly sensory processing in function. This is also known as the Classical Sensory Afferent Function of TRP Channels. Alternatively, TRP could also propagate skin pathological sensation through Neurogenic Inflammation involved mainly TRPV1, TRPV3, TRPV4, TRPA 1 and TRPM [10]. Anatomically, nerve endings penetrate into the epidermis which composed mainly of keratinocytes, it is suggested that keratinocyte through TRP receptors sense directly to the noxious stimuli. Since, the effects of TRP channel mediated depolarization is not confined to neurones, membrane depolarization in keratinocytes can affect cellular process such as ATP release, nitric oxide release or calcium flux through Orai family channels [10,11]. The interaction of neuronal expressed TRPV1 with skin is bidirectional, involving both sensory and efferent activity. Non-neurogenic Inflammation due to defective epidermal barrier, cytokines and inflammatory mediators, without neurogenic involvement could also results from sensitive skin [11]. The latter involved, apart from TRPV1 and TRPA1, other TRP channels like TRPV 3, TRPV 4 and TRPM 8 [10,11]. These three pathways are not mutually exclusive and may act simultaneously and synergistically resulted in an orchestrated attack on the skin including its nervous system with the transmission of the warning signals of itch, pain, erythema, and swellings. The followings discussed in details, the TRP channels involved in the pathology of SSS.

TRPV1

TRPV 1 vanilloid subfamily member is found mostly on neuronal endings of sensory fibres, but also in skin cells like keratinocytes, fibroblasts, mast cells and the endothelial cells of blood capillaries in skin dermis. Many of these free nerve endings are in close proximity to small blood capillaries and mast cells in the skin which plays a sentinel role in skin neurogenic inflammation (**Table 1**). The cell-rich dermis of the skin also provides a transit for these peripheral nerve endings to protrude into the epidermis with keratinocytes [12]. TRPV receptors have also been located in the CNS such as the spinal cord and the thalamus, cerebral cortex of the brain. The

functional co-existence of TRPV receptors in the keratinocytes of the skin epidermis and afferent neurones have reviewed new understanding that the outermost layer of our body, the epidermis which serve as an interface of our bodily structures with the environment may well be a functional part of our extended nervous system. The epidermal keratinocyte with its well armoured TRP receptors channels form a key part of the sensory system and directly initiate nociceptive response [13]. This is the proposed TRPV1 neurogenic pathway. Known noxious chemical and physical agents like Ultraviolet light, thermal stimuli, low pH, endogenous bradykinin, Nerve Growth Factor (NGF), lipids and metabolites of arachidonic acid and ATP activate the TRPV 1 receptor in the keratinocyte it cause the release of PGE 2, IL 8 and upregulate COX 2, it also induces the release of proinflammatory mediators [14,15]. The nerve free endings of the afferent neurones possess TRPV 1 receptors which then activated to secret Substance P (Sub P) in the dorsal root ganglion neurons, SP is known to be a potent neurotransmitter which also triggers the glutamate pathway and by calcium influx through the NMDA, calcium channel propagate the sensation of itch [16]. Apart from SP, the pruritogen, Calcitonin Gene Related Peptide (CGRP) and Tachykinin were also produced. Similarly, SP will then also provoke a cascade of local tissue inflammatory responses through a number of mediators, cytokines and molecules which are known to result in itches [17-20]. This is referred to TRPV1 neurogenic inflammatory pathway of itch. The damaged keratinocyte produced PEG 2 and IL 1 locally in the epidermis causing delayed epidermal barrier recovery. Further noxious stimulants including pathogens through a defective barrier will invade the cellular epidermis. This results in non-neurogenic inflammatory response through TRPV1 [21]. The cellular response would then be magnified until the threshold of itch sensation through neuronal depolarization reached the CNS. The final mediation of the pathway in the CNS is still unclear. If no early interventional or remedial mechanism is put in place, the uncontrolled sensation of skin discomfort of itch, burning, and tingling will persist complicated secondary inflammatory sequelae of erythema, oedema and pain. This may well explain the clinical presentation of the SSS when the patient complained of itchy, painful facial swelling with erythema when the TRPV 1 is activated by irritant cosmeceuticals. Interestingly, TRPV3; a relative of TRPV 1; was also found in abundance and densely populated in the epidermal keratinocyte and studies also showed they are actively involved in this TRP mediated pathway of itch and pain [22]. Both sensitizing and desensitizing compounds are known to interact with TRPV receptors: capsaicin, capsazepine, ruthenium red, lactic acid, Sodium Laura Sulphate (SLS), DMSO, menthol, camphor, ID 1609, phenoxyethanol, clotrimazole and the drug topical retinoid and tacrolimus are used to treat acne vulgaris and Atopic Dermatitis respectively [23,24]. The analogues and derivatives of these compounds and its natural equivalents should be carefully and systemically test and studied both; in vitro and in vivo; to see its effects on alleviating the signals of itch and hence these symptoms in SSS [25-27].

TRPV 3

TRPV3 is highly expressed in epidermal keratinocytes and reported to have its highest density. It has not been reported to be located in the free endings of the afferent neurons [28,29]. It's activation has an antiproliferation and pro-apoptosis effects of epidermal keratinocytes. Furthermore [30], activation of TRPV3 causes release of NO from keratinocytes which have significant effects on stimulated wound healing and keratinocyte migration [12,13]. Interestingly, constitutively active gain-of-function mutation TRPV3Gly573Ser causes loss of hair and atopic-like dermatitis which also demonstrate intense itching [31]. TRPV3 like its relative TRPV1 thus participates in the mediation of proinflammation [32]. It has been suggested that TRPV 3 may also be involved in the pathogenesis of itch in SSS and related dermatosis through its pro-inflammatory mediators [32-35]. TRPV 3 was believed in "indirect" skin keratinocyte communication with sensory neurones. This may happen in SSS [12].

TRPV4

TRPV4 is found in keratinocyte and densely populated in afferent neurones endings. They are suggested also to have involved in the neurogenic transmission of itch and pain [12,36]. Interestingly, the TRPV 4 perception of itch has been found in an experiment to be facilitated by TRPV1 channels [37-39].

TRPA 1

TRPA 1 is a subfamily of TRP of the ankyrin family. It is usually referred to as the cold receptor as it is readily activated by cold. TRPA 1 was demonstrated to be heavily present on expressed nociceptive sensory neurons [40]. TRPA 1 is closely related both functionally and anatomically to TRPV1 in the processing and mediation of various environmental noxious signals like cold, pain and itch [12]. It involves in the afferent processing of the signals of cold through calcium influx. This implies TRPA 1 has a direct and initial activity in the transmission of nociceptive signals through neuronal depolarisation in SSS. A number of irritants are known to interact with TRPA 1 like mustard oil, formalin, nicotine, allyl isothiocyanate, cinnamaldehyde, icilin and HC030031 can evidently modulate the sensation of itch, pain and cold (**Table 2**). Recent studies have further suggested that the pruritogen-sensing G protein-coupled receptors, MrgprA3 and MrgC11 ligands associated itch is TRPA1 mediated. Moreover, Morita and colleague showed that HTR 7 receptor activation triggers Serotonin and, SSRI evoked itch by promoting opening of the TRPA1 channels [41]. Acute itch triggered by Serotonin and SSRI uptake inhibitor required both HTR 7 and TRPA1, hence, it was proposed that HTR 7 and TRPA1 is functionally coupled especially in elicit itch. Finally, the newly discovered IL-31 was discovered to be closely assembled both anatomically and functionally with TRPA1 and TRPV1 in Atopic Dermatitis induced itch [42]. At present, more emerging evidences has suggested that TRPA1 is more directly involved and played a

more crucial role than TRPV1 in the propagation of itch in the itchy pathway [43]. TRPA1 function as an effective integrator of excitatory signalling pathway [12].

TRPA1 also has epidermal regulatory function and pro-inflammatory properties like TRPV1. This can be mediated neurogenic and non-neurogenically. TRPA 1 has been shown to maintain epidermal homeostasis and promote epidermal barrier repair. The latter was achieved through the cold receptor property of TRPA 1 [44]. Icillin which activates TRPA 1 induced keratinocyte extracellular matrix proteins changes and increased intracellular calcium enhanced keratinocyte differentiation and maintain epidermal barrier. On the other hand, HC 030031; a potent TRPA 1 antagonist; reverse the above and disrupt epidermal barrier homeostasis [45]. TRPA1 is also shown to be involved in the initial triggering of non-neurogenic inflammation [45]. Topically applied cinnamaldehyde induced skin inflammation through TRPA 1 resulting oedema and leukocyte migration has both neurogenic and non-neurogenic components: sensitised TRPA1 channels in afferent sensory neurones caused SP released in turn activates NK1 tachykinin receptors [12]. NK1 tachykinin is a well-documented itch mediator and in this case NK1 tachykinin release and resulting swelling is readily blocked by aprepitant, an inhibitor of NK1 tachykinin receptors suppressed oedema and inflammation resulted from SP release while; on the other hand; TRPA1 through non-neurogenic inflammation stimulate dendritic cell migration to lymph nodes and white cell migration resulting into tissue swelling was inhibited by TRPA1 inhibitors [46]. Both neurogenic and non-neurogenic proinflammatory function of TRPA1 has great significance in understanding SSS and related contact dermatitis. For example, oxazolone has been shown to activate recombinant TRPA1 resulting in features of contact dermatitis [47]. Whereby applying the same oxazolone-induced contact dermatitis model, blockade and genetically TRPA1 deletion have decreased skin oedema, white cell infiltration and scratching behaviour and epidermal hyperplasia in mice with significant reduction in the amount of proinflammatory cytokines, NGF, 5-HT and SP [48]. Similarly, the known contact allergen of poison ivy; Urushiol; induced itchy dermatitis after contacts are also found diminished in TRPA1 depletion in TRPA1 KO mice. All these evidences strongly suggested that TRPA 1 has indeed a fundamental pivotal role in the initiation of itch and associated cutaneous inflammation. TRPA 1 may have a pathogenetic role in SSS through its neurogenic and non-neurogenic inflammatory mechanism [48].

TRPM

TRPM belong to another sub-family of TRP channels closely related to skin functions, especially in melanocyte biology. In the context of neurogenic skin disease, TRPM8 is most important as it is shown to be involved in keratinocyte function and epidermal homeostasis. TRPM was found mostly in melanocyte and keratinocyte [49]. Similar to TRPA1, TRPM8 is activated by cold, menthol, eucalyptol and icilin [12]. It may postulate that TRPM 8 may act like TRPA1 as a neurogenic pathway of itch and its related modalities [50,51]. TRPM8 is also involved in skin repair and barrier function maintenance as it is shown that when menthol is applied to severe injuries on the skin of the back of the mice, there is accelerated healing, but there is an inhibition by the TRPM8 antagonist N-(4-t-butylphenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1(2H)-carboxamide (BTCT) [49].

TRP Channels and SSS

TRP channels play a central role in the perception and pathophysiology of sensitive skins While it is widely recognised that TRPV1 is the major receptor involved, TRPV3, TRPV4, TRPA1 and TRPM8 may all closely involved in the neurogenic transmission and inflammation of such perceptions [1]. The newly discovered endogenous pruritogens, HTR7, MrgprA3, MrgC11 ligands and IL-31 mediated itch further substantiate this claim. Since TRPV3 and TRPM8 are not found in the afferent neurons, but they are found in epidermal keratinocytes. They are more involved in non-neurogenic skin inflammation or secondary recruitment after the neurogenic activation by TRPA1 and TRPV1. TRP channels have a complex combination and synergistic end organs effects in promoting inflammation and propagation of the sensation of itch, pain and burning to CNS. A great number of activators as aforesaid, when applied in vivo and in vitro give similar a presentation to SSS. Together with its actions on epidermal homeostasis, inflammation, and cutaneous immunological functions, TRP channels unequivocally are pathogenic on sensitive skin. The TRPA1, TRPV1, TRPV3, TRPV4, and TRPM8 are ideal pharmacological therapeutic targets in sensitive skins.

Current Management of SSS

The current management of sensitive skin is suboptimal and unsatisfactory due to, inadequate recognition of presentation and understanding of the pathogenesis condition. It is not uncommon to see doctors who fail to realise the intimate and crucial relationship between skin and nervous system in the translation of symptoms or perceptions of itch, pain and tightness as a result of swellings. Secondary, till now, no specific targeted pharmacological therapy has been proven to treat SSS in a double-blinded evidence-based manner. This poorly managed group of patients will become chronic sufferers as these sensitizers (TRP channels sensitizers) are unlikely to be identified and removed from their daily skin care rituals. They become shopper between different doctors, pharmacy and health care systems especially herbal medicines. Topical steroids are frequently tried. Abuse and misuse of steroids not only results in the waste of resources but also worsen the defective epidermal barrier; steroid induced skin atrophy and steroid induced Rosacea are not uncommonly seen.

Confirming the diagnosis is mandatory for the management of SSS. This can be assisted by a detailed clinical history and recording the types, intensity and aggravating factors of the subjective perceptions. The sites of the discomfort should be mapped out. Associated diseases of the nervous system and neuropathies and dermatological condition should be noted.

Lactic acid stinging test, occlusion tests, behind-the-knee tests, washing immersion tests can help evaluate and quantify itch. A questionnaire "Score d'Irritabilite Global Local" (SIGL) in French was available. Since SSS is subjective perception as reported by patients, some authors regarded this type of patient self-reported questionnaire as the best method to diagnose sensitive skin [1]. If the known triggering irritant is known, it should be avoided. Topical steroids should not be used [1]. Topical moisturisers are useful, especially they help to protect the defective epidermal barrier and also those with lipids and non-saturated fatty acids components may supress inflammation through TRPV 1. Topical substances that include camphor, menthol can relief the distressing sensation through TRP channels. A new combination TRPV1 inhibitor formula consisted of 4-t-butylcyclohexanol and licochalcone A-rich licorice extracts have been used successfully in a rapid way to control the symptoms of SSS. Low fluence laser and light therapy act through the TRPV1 are also reported effective [52]. Topical calcineurin inhibitor which is used to treat Atopic Dermatitis is reported to be useful to suppress the itch in a women population through TRPV1 [53]. However, at present, no topical or systemic TRPA1 agonist or antagonist was available to treat sensitive skins [54]. As mentioned, all compounds used were not studied in a double blinded controlled method. Serlopitant, a HT blocker, found to be useful in stopping itch through the NK1 tachykinin pathway was studied in a controlled trial in SSS but again this is not a direct blockade of TRPA1 or TRPV1 and the TRP channel neurogenic pathway of itch was not tested. Last, not the least, there are limited studies reporting the TRP channels in the CNS comp especially in the DRG, spinothalamic tracts, thalamus and cerebral cortex and its activation, inhibition and factors affecting its function [55]. Admittedly, itch like other noxious perceptions are finally relayed to our cerebral cortex to give us the distressed, sometimes frustrating feelings.

Looking into the Future

This year 2017 marked the twenty year anniversary of discovery the first TRP channels by Julius. The understanding of the TRP channels – afferent neurones – CNS connections and its associated epidermal pathologies provide the basis and therapeutic insight into the management of many skin diseases which are obscure in the past [55].

Table 2. Activators, Agonists and Antagonists of TRP Channels.

TRP Channels	Compounds interact with TRP channels
TRPV1	Capsaicin (1) Resiniferatoxin (1) Capsazepine (3) Ruthenium red (3) UV light (1) Thermal stimuli (> 43C) (1) Acidic condition (Ph < 5.9) (1) Endogenous bradykinin (1) Nerve growth factor (1) Endogenous cannabinoid lipids like anandamide (1), Arachidonyly serotonin (3) Arvanil (1) 2 Aminoethyl diphenylborinate (2-APB) (1) Metabolites of Arachnidonic acids (1) ATP (1) Histamine (1) Trans-tert-butyl cyclohexanol (TTBC) (ID 1609) (2) Lactic acid (1) Sodium Lauryl Sulphate (1) DMSO (1) Menthol (1) Clotrimazole (1) Retinoids (1) Tacrolimus (1)
TRPV3	Nitric oxide (1) Moderate Thermal heating (32C) (1) Plant derived monoterpenoids: menthol, camphor, carveol, thymol, eugenol, citral (1) Incensole acetate(1) Plant cannabinoids like tetrahydrocannabinol (1) 2-APB (1) Unsaturated free fatty acids (1) Chloroquine (1) Clotrimazole (1) Hypoxia (1) Farnesyl Pyrophospate (FPP) in cholesterol synthesis (1)
TRPA1	Mustard oil (1) Nicotine (1) Cinnamaldehyde (1) Cold (1) Allyl isothiocyanate (1) Acrolein (1) Tear gas components (1) Formaldehydes (1) MrgA3, MrgC11 (1) Methylglyoxal (1) Chloroquine (1) Endothelin 1 (1) Compound 48/80 (1) Pruritogen sensing G protein Coupled receptor (1) Oxazolone (1) Urushiol (1) Icilin (1) Serotinoin (1) SSRI uptake inhibitor (1) Anaethesia like Propohol, Isofluorane and Lidocaine (1) Fenamate NSAID drugs Cannabinoids (1) Endogenous protein Thymic Stromal Lymphopoietin (TSLP) (1) Bile acids (1)
TRPM8	Cold (1) Menthol (1) Eucalyptol (1) Icilin (1)

Activators=1, Agonist=2 and Antagonist=3

In the development of TRP blockade in SSS, all TRP channels, TRPV1, TRPA1, TRPV3 TRPV4 and TRPM8 activators, antagonists or blockades should be considered. TRPV1 antagonist has been reported to be effective in diminishing symptoms in sensitive skin; TRPA1 manipulation has evidence, at least theoretically, useful in stopping itch and pain in SSS. Examples are cryogenic spray, menthol, cinnamaldehyde and icilin has been used to stop the recalcitrant itch in sensitive skins. A list of TRPV1, TRPV3, TRPV4 and TRPA1 activator, agonist or antagonist was shown in **Table 2**.

Conclusion

Ontologically, the human beings outermost layer-skin is derived from the same germ layer as the nervous system including the brain, TRP channels like progenies were distributed among these two important organs. TRP not only helps to explain condition which has a shared pathogenesis of skin and nervous system disease like SSS. But also show the anatomical similarity and differentiation of the same original structure of ectoderm on the body. It is likely that more of this kind of channels and receptors may be discovered in the near future. More research and efforts should be mandated to study potential pharmacological agents that interact with TRP channels especially TRPA1 in dermatological and nervous system pathological condition.

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