Mini Review Article

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Targeting the Receptor at Synapse of Keratinocyte and Peripheral Nerve Ending: A Therapeutic Hope for Post-Burn Pruritus

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Abstract

Chronic itch or Pruritus is an unpleasant sensation that provokes the desire to scratch. In post burn patients, it is a significant health burden with few effective treatments. Pruritus is a common distressing consequence of post-burn scars which affects burn survivors' quality of life by causing sleep disturbance, daily activity impairment, and psychological problems. The mechanism of such abnormal scars with pruritus is not yet clear. The field of pruritus research is a dynamic field which involves neural component and various receptors at skin. The receptor present at the synapse of keratinocytes and peripheral nerve ending are responsible for itching. Many recent studies have worked to define the various receptors and the itch mediations in skin. However, considering that post-burn patients mainly report itch to be localized in the burn scars, spontaneous itch might be strongly based on peripheral input. The detailed characteristic and the factors for persistence of pruritus in post burn patients have not yet been clearly understood. Experimental evidences suggest that transient receptor potential (TRP) channels in skin and their expression patterns, activation mechanisms play regulatory roles in pruritus pathogenesis. In this article author collected the pruritus related data from post burn pruritus patients, isolated keratinocytes checked the receptor expression by immunocytochemistry and discussed the complex interplay between the central and peripheral factors that causes pruritus. It would be helpful to identify novel anti-pruritic agents that target the molecular itch pathogenesis pathways and the clinical assessment for burn patients with pruritus.

Keywords: Peripheral Nerve Ending, Keratinocytes, Pruritus, TRPV Receptor

Introduction

Pruritus or itch is a more or less voluntary activity and defined as an unpleasant cutaneous sensation associated with urge desire to scratch. Pruritus is distinct from that of pain and pruriceptive system consists of itch-inducing peripheral mediators (pruritogens), itch-selective receptors (pruriceptors), sensory afferents and spinal cord neurons, and defined, itch-processing central nervous system regions display complex, layered responses to itch. The peripheral nerve ending forms synapse with keratinocyte of skin. The receptors present at this synaptic junction are important for itch related phenomenon. The functional characteristics of the large family of transient receptor potential (TRP) channels in skin and their expression patterns, activation mechanisms, regulatory roles, and pharmacological sensitivities are expected to be key players in pruritus pathogenesis [1].

TRP channels are located at the cell surface and these are multifunctional signalling molecules. The defect in TRPV gene encode defective TRP channels and causes numerous diseases and their role in health and diseases has focused on pain research and clinical indication. The inflammatory mediator bradykinin (which induces pain via activation of bradykinin B2 receptors located on the nociceptors) is also implicated in the pathogenesis of pruritus and certain members of the large family of inflammatory immune cell-derived interleukins (IL 2) induces itch by activation of a subpopulation of cutaneous C-fibers that are chemo sensitive to histamine and bradykinin [2]. Histamine is mostly released from activated mast cells and epidermal keratinocytes, and acts on specific H-receptors and is the best-known pruritogen [3]. Patients suffering from post-post burn pruritus show distinctive clinical and histopathological features, such as prominent mast cell deposition and thin collagen bundles, in comparison with burn patient without pruritus [4]. In post burn pruritus, higher intensity of itching has been associated with depth of the wounds and specific body locations but these differences are not well understood [5]. Pruritus induces scratching which can cause wound infections and interrupt the proper wound healing process. Patients suffering from post-burn pruritus show distinctive clinical and histopathological features, such as prominent mast cell deposition and thin collagen bundles. However, patients without pruritus have thick collagen bundles with basket-weave patterns.

Hypertrophic scars or keloids usually cause pruritus and show

an abnormal ratio of type I collagen to type III collagen, suggesting that altered collagen fiber types are related to the itching. Hence it would be worthwhile to explore the pattern of receptor expression and their functional activities in post-burn pruritus in comparison to burn patient without pruritus. The mechanism of abnormal scars with pruritus, involvement of transient receptor potential (TRP) channels in skin and their expression patterns, activation mechanisms in pruritus is not yet clear [6]. To understand the production of pruritogens at the peripheral nerve ending and the expression pattern of different TRP channels in skin cells of burn patient is a crucial need to elucidate mechanisms for pruritus associated with burn injury. The markers of pruritus and the molecular mechanism of pruritus, help to identify novel anti-pruritic agents that target defines the molecular itch pathogenesis pathways and the vital clinical importance evaluate the clinical assessment for burn patients with pruritus.

Materials & Methods

The preliminary study has been done with the co-operation of patients with post burn scars visit to Burns Hospital. The study protocol was approved by institutional ethics committee. All patients were asked whether they felt pruritus on their burn scars and about the severity of pruritus. The patients with pruritus will be asked to describe the severity of pruritus based upon the Leuven Itch Scale [7]. The burn scars were assessed using the Patient Scar Assessment Scale (PSAS) which consists of pain, pruritus, color, stiffness, thickness and irregularity. With the proper consents from patients, skin samples (6-10 mm punch biopsy) were obtained from 2 different sites: one from a burn scar and the other from normal skin. Epidermal thickness and other dermatological studies were done using haematoxylin eosin staining. The expression of TRPV receptor expression is checked by immunocytochemistry. Skin cells such as keratinocyte and melanocyte will be isolated from patients skin tissues (with and without pruritus) and TRP channel function in individual cells would be tested by sequential application of the agonists or antagonist for TRP channels such as capsaicin and allyl isothiocyanate. Future experiment would be concentrated upon the regulatory pattern of TRP channels which will help to determine a specific therapeutic approach for post-burn pruritus.

Results and Discussion

The field of pruritus research is a dynamic field and many advances have been made so far this decade. Many recent studies have worked to define the various receptors and the itch mediations in skin. However, considering that post-burn patients mainly report itch to be localized in the burn scars, spontaneous itch might be strongly based on peripheral input.

The data from four recent operation restores patient camp no-16,17,18,19 indicated that 31 out of 131 patients had post burn pruritus as shown in figure 1.

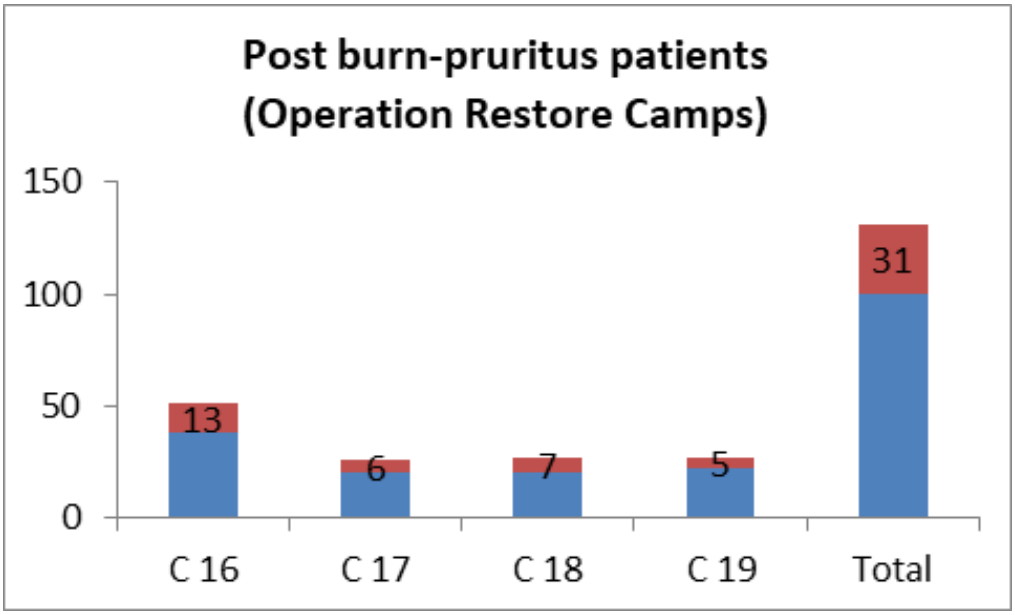

Figure 1: Pruritus patients of four different camps at Burn hospital. Different camp numbers are C16, C17, C18 and C19. Total patients are 131 and pruritus patients were 31.

The detailed characteristic and the factors for persistence of pruritus in post burn patients have not yet been clearly understood. Hence it will be meaningful to conduct research on developing a treatment with an antagonist against the specific transient receptor potential channel that is intimately related to post-burn pruritus. Medical treatment by using receptor antagonist alleviate itch or psychological therapies which might be effective in post-burn pruritus. It will be a revolution for treatment of chronic pruritus. Pruritus is a common distressing consequence of post-burn scars that affects burn survivors' quality of life by causing sleep disturbance, daily activity impairment, and psychological problems. If a successful anti-itch therapy can be explored as treatment option, post-burn patients can carry normal life. The mediators identified in the animal studies and in human cell lines again the TRPV receptor is RN 1734, by various research groups [8, 9].

It will be used for human study and it may prove the effective targets in future therapies. Co-relation with antagonist-itch relieves and the pressure evoked by scratching for itch relief can be compared. In future, investigating of itch-related behavior of TRP channels and evaluation of novel TRP-channel-acting

pharmacological agents and to identify novel candidate anti-pruritic agents or "itch killer" that target defines the molecular itch pathogenesis pathways and the vital clinical importance. Identifying the novel anti-pruritic agents that target the molecular itch pathogenesis pathways will reduce the post-burn pruritus. With effective treatments, the unpleasant sensation that provokes the desire to scratch will be diminished and patient will carry normal life.

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