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Review
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Neuroimmunological Mechanism of Pruritus in Atopic Dermatitis Focused on the Role of Serotonin

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Abstract

Although pruritus is the critical symptom of atopic dermatitis that profoundly affect the patients' quality of life, controlling and management of prurirtus still remains as unmet needs mainly due to the distinctive multifactorial pathogenesis of pruritus in atopic dermatitis. Based on the distinct feature of atopic dermatitis that psychological state of patients substantially influence on the intensity of pruritus, various psychotropic drugs have been used in clinic to relieve pruritus of atopic dermatitis patients. Only several psychotropic drugs were reported to show real antipruritic effects in atopic dermatitis patients including naltrexone, doxepin, trimipramine, bupropion, tandospirone, paroxetine and fluvoxamine. However, the precise mechanisms of antipruritic effect of these psychotropic drugs are still unclear. In human skin, serotonin receptors and serotonin transporter protein are expressed on skin cells such as keratinocytes, melanocytes, dermal fibroblasts, mast cells, T cells, natural killer cells, langerhans cells, and sensory nerve endings. It is noteworthy that serotonergic drugs, as well as serotonin itself, showed immune-modulating effect. Fenfluramine, fluoxetine and 2, 5-dimethoxy-4-iodoamphetamine significantly decreased lymphocyte proliferation. It is still questionable whether these serotonergic drugs exert the immunosuppressive effects via serotonin receptor or serotonin transporter. All these clinical and experimental reports suggest the possibility that antipruritic effects of selective serotonin reuptake inhibitors in atopic dermatitis patients might be at least partly due to their suppressive effect on T cells. Further studies should be conducted to elucidate the precise mechanism of neuroimmunological interaction in pruritus of atopic dermatitis.

Key Words: Pruritus, Atopic dermatitis, Neuromediator, Serotonin, T cells

Pruritus is defined as an unpleasant sensation eliciting the urge to scratch. It is one of the signature symptoms in inflammatory skin diseases. Atopic dermatitis (AD) is one of the most pruritic skin diseases and pruritus is an essential feature in diagnosis and treatment of AD (Koblenzer, 1999). Long-lasting pruritus has a profound impact on the patients' quality of life (Metz *et al.*, 2011). In many cases, patients scratch the skin lesions to cause erosions, ulcerations, bleeding, and lichenification which can aggravate AD symptoms in turn. The sleep disturbances following prolonged nocturnal scratching and psychological difficulties such as cicatrization and social isolation also result in dramatic impairment in the quality of life in AD patients (Buske-Kirschbaum *et al.*, 2001). Thus, proper treatment of pruritus is the critical part of therapeutic approach to AD.

Based on early studies, pruritus was regarded as a low-intensity pain for a long time. Nowadays, it is clear that the sensation of pruritus is distinct from the sensation of pain and there exists a sensory system for pruritoception that is different from the sensory system for nociception (Andrew and Craig, 2001; Paus *et al.*, 2006; Handwerker and Schmelz, 2009). Pruritus can be triggered by various endogenous and exogenous stimuli via free endings of specific nonmyelinated, slow-conducting C-type nerve fiber in the epidermis and dermis (Ständer *et al.*, 2002). The stimuli run along the dorsal root ganglion via the spinal cord and reach different areas of the cortex, where the scratching reflex is initiated.

A number of reports indicated that skin immune system is closely related to the provocation and intensity of pruritus in AD patients. In this review, the neuroimmunological mechanism of pruritus in AD would be discussed based on the reports about the antipruritic effects of several psychotropic drugs, especially focused on the role of serotonin in skin.

SPECIFIC FEATURES OF PRURITUS IN ATOPIC DERMATITIS

Although the pathophysiology of pruritus in AD has not been fully defined yet, a number of reports demonstrated that

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pruritogenic mechanisms involved in AD are different from those of normal pruritus. The skin lesions of AD often have increased density of cutaneous nerve fibers (Tobin *et al.*, 1992; Urashima and Mihara, 1998). AD lesional and nonlesional skin showed increased substance P-positive and calcitonin gene related peptide (CGRP)-positive fibers associated with increased mast cell-nerve fiber contacts (Järvikallio *et al.*, 2003; Elenkov, 2004). In addition, the skin of AD patients have reduced pruritus threshold and prolonged pruritus duration to pruritic stimuli as compared with healthy skin, resulting in a higher tendency to pruritus upon stimulation (Morren *et al.*, 1994).

So far, many laboratory and clinical data indicated that a number of genetic, environmental and psychological factors are related to pruritus in AD (Pastar *et al.*, 2005; Weidinger *et al.*, 2008). A group of pruritogens including inflammatory lipids, cytokines, neuropeptides, neurotransmitters such as histamine and serotonin (5-hydroxytryptamine, 5-HT), proteases, proteinase-activating receptors, and opioid peptides appears to be related to pruritus in AD (Darsow *et al.*, 1997; Steinhoff *et al.*, 2006; Ständer *et al.*, 2008; Lee, 2010). Among these factors, histamine has been the most well-known pruritogen. Histamine was found at high concentrations in AD lesions and most of the cells involved in the inflammatory responses express the histamine 1 receptor (H1R) and histamine 2 receptor (H2R)(Mommert *et al.*, 2011). There is a specific chemosensitive subpopulation of C-fibers that mediate histamine-induced pruritus (Schmelz, 2001; Schmelz *et al.*, 2003). In this context, H1R antagonists have been tried and demonstrated to reduce pruritus in numerous clinical trials (Sugimoto *et al.*, 2004; Paus *et al.*, 2006). However, in AD patients, antihistamines showed only limited clinical efficacy to pruritus (Klein and Clark, 1999) suggesting that histamine is unlikely to be a major peripheral mediator of pruritus in AD (Rukwied *et al.*, 2000).

Recently, the fourth histamine receptor (H4R) brought histamine back into focus in the pathophysiology of pruritus in AD. Several studies showed that the H4R, which is differentially expressed on immune and nonimmune cells, plays an important role in pruritus of AD patients (Dijkstra *et al.*, 2007; Gutzmer *et al.*, 2009). Pruritus was selectively inhibited by the treatment with a H4R antagonist in a Th2 cell-mediated mouse skin inflammation model that mimics several features of AD (Cowden *et al.*, 2010) or in H4R knockout mice (Dunford *et al.*, 2007).

Despite of the newly discovered role of H4R in pruritus of AD lesion, it is still accepted that histamine is not the sole mediator of pruritus in AD and mediators other than histamine such as cytokines and neuropeptides may be involved in induction of intractable, recurrent pruritus in AD. This assumption is supported by the evidence of histamine-independent pruritus-specific fibers in the skin (Nakano *et al.*, 2008).

ANTIPRURITIC EFFECTS OF IMMUNOMODULATING THERAPY IN ATOPIC DERMATITIS

Controlling and treatment of chronic pruritus is one of the major unmet needs in the therapeutic approach to AD. Because of the multifactorial pathogenesis of AD, no specific, universally effective and well-tolerated antipruritic agent for AD has been developed yet (Lee, 2010). Until now, management of pruritus in AD is mainly confined to imunomodulators such as glucocorticoids, cyclosporin A and topical calcineurin inhibitors (tacrolimus and pimecrolimus) (Wahlgren *et al.*, 1990; Hoare *et al.*, 2000; Hanifin *et al.*, 2001; Luger *et al.*, 2001). These immunomodulating therapies applied in AD often succeed in reducing pruritus via suppressing the inflammatory mechanisms underlying the induction of pruritus (Yosipovitch *et al.*, 1996). The reports that cyclosporin A treatment reduced pruritus in AD patients clearly showed that interleukin-2 and T cells are at the center of AD pruritus (Wahlgren *et al.*, 1990). Even a single intracutaneous injection of IL-2 resulted in intermittent local pruritus perception in AD patients (Wahlgren *et al.*, 1995; Darsow *et al.*, 1997).

ROLE OF SKIN T CELLS IN THE PATHOPHYSIOLOGY OF PRURITUS IN ATOPIC DERMATITIS

The skin of AD patients show infiltrating $CD11c^+$ dendritic cells and $CD3^+$ T cells (Novak and Leung, 2011) mainly composed of $CD4^+$ and cutaneous lymphocyte associated antigen $(CLA)^+$ T cells (Leung and Bieber, 2003; Leung *et al.*, 2004). The infiltrates predominantly consist of interleukin 4 -producing Th2 type cells in the initial phase of AD, whereas chronic lesions frequently show infiltrates with Th1 type (Leung and Bieber, 2003). It has been reported that Th2-type cytokines are involved in the interplay between nerves and T lymphocytes indicating the roles of cytokines in pruritus (Sonkoly *et al.*, 2006; Cevikbas *et al.*, 2011). However, a recent report from biopsies taken from atopy patch test revealed that in addition to $CD4^+$ T cells, $CD8^+$ T cells might play a pivotal role for the development of eczema (Hennino *et al.*, 2011).

Recently, a novel T cell-driven cytokine interleukin 31(IL-31) has been found to be significantly upregulated in pruritic AD patients compared with healthy, nonatopic subjects (Sonkoly *et al.*, 2006). Actually IL-31 induced severe pruritus and dermatitis in transgenic mice (Sonkoly *et al.*, 2006). The sources of IL-31 include the activated skin infiltrating CLA-positive T cells (Bilsborough *et al.*, 2006). All these results back up the earlier reports suggesting that skin-infiltrating T cells might play a major role in pruritus in AD (Wahlgren *et al.*, 1990; Greaves and Khalifa., 2004).

There is a specific type of T cells in the skin epidermis and intestinal epithelia, the $\gamma\delta$ T cells. In contrast to the classical $\alpha\beta$ T cells, $\gamma\delta$ T cells have limited specificities of T cell receptor (TCR), unusual dendritic shape, and functions distinct from $\alpha\beta$ T cells in many ways. These cells have been found to play crucial roles in tissue homeostasis and damage repair by recognition of damaged self (Jameson *et al.*, 2002; Strid *et al.*, 2009), whereas $\alpha\beta$ T cells function in foreign antigen recognition. Epithelial $\gamma\delta$ T cells express special costimulatory molecules such as junctional adhesion molecule-like protein (JAML) (Witherden *et al.*, 2010). Once activated, epithelial $\gamma\delta$ T cells express cytokines that promote inflammation and stimulate repair of the skin tissue (Sharp *et al.*, 2005). However, it is unknown what molecules are recognized by $\gamma\delta$ T cells and by what mechanisms $\gamma\delta$ T cells are activated.

Interestingly, activation of H4R on Th2 cells increased the production of IL-31, which is one of important inducers of pruritus in AD (Gutzmer *et al.*, 2009), suggesting the possibility that receptors of neuromediators might be involved in the activation process of skin T cells.

INTERACTIONS BETWEEN NERVOUS SYSTEM AND IMMUNE SYSTEM IN ATOPIC DERMATITIS

In the skin, the nervous and immune systems bidirectionally interplay via the action of neuromediators (neuropeptides and neurotransmitters) that are released by skin nerves and the immune cells (Luger, 2002; Straub, 2004). The cells of both systems are able to release neuromediators and respond to them via specific receptors expressed on their surface. For instance, skin immune cells such as mast cells and dendritic cells release neuropeptides which induce activation of nerve ending, vasodilatation, and plasma extravasation (Roosterman *et al.*, 2006). In turn, neuropeptides such as vasoactive intestinal peptide (VIP) and CGRP modulate the functions of macrophages and T cells (González-Rey *et al.*, 2007) and langerhans cells (Cevikbas *et al.*, 2007) respectively, while substance P affects lymphocyte proliferation and mast cell degranulation (Turner *et al.*, 2007). Thus it seems quite reasonable that neuromediators are involved in the pathogenesis of pruritus in AD (Roosterman *et al.*, 2006). Actually, stressed patients with AD had increased numbers of 5-HT-receptive mast cells (Lonne-Rahm *et al.*, 2008).

ANTIPRURITIC EFFECTS OF PSYCHOTROPIC DRUGS IN ATOPIC DERMATITIS AND THE ROLE OF 5-HT IN NEUROIMMUNE INTERACTION

Another distinct feature of AD is the substantial influence of psychological state on the intensity of pruritus. The majority of patients with AD reported that psychological stress aggravated their pruritus, suggesting that pruritus might be closely related with emotional distress in AD (Wahlgren, 1992). In this context, various psychotropic drugs have been tried in clinic to relieve pruritus. However, only several psychotropic drugs showed real antipruritic effects in AD patients. Table 1 summarizes the Ki (binding affinity) values of the antipruritic psychotropic drugs to receptors and transporters for various neurotransmitters. The opioid receptor antagonist naltrexone showed antipruritic effect in patients with AD (Heyer and Hornstein, 1999). A tricyclic antidepressant doxepin showed antipruritic effect topically and systemically for its additive antihistaminic and anticholinergic effects (Drake and Millikan, 1995). Tricyclic antidepressant trimipramine, that antagonizes H1 receptor and H2 receptor, reduced nocturnal scratching in patients with AD (Savin *et al.*, 1979). Bupropion is an antide-

Table 1. Binding affinities of antipruritic psychotropic drugs to receptors or transporters for various neuromediators

Name	Mechanism	Ki (nM)								
		Histamine receptor 1	Opioid receptor	Cholinergic, muscarinic receptor	Adrenergic receptor	Norepinephrine transporter	Dopamine Transporter	Dopamin receotor 2	5-HT transporter	5-HT receptor
Doxepin	Tricyclic antidepressant	0.24		23	α1: 23.5 (brain) α2: 1,270 (brain)	29.5	>10,000	360 (brain)	68	1A: 276 (brain) 2: 27 (brain)
Trimipramine	Tricyclic antidepressant	1.4 (cortex)				2,450	3,780		149	
Bupropion	Atypical antidepressant	>10,000 (cloned)		>10,000	α1: 4,200 (brain) α2: >10,000 (brain)	>10,000	541	>10,000 (brain)	>10,000	1A : >10,000 (brain) 2 : >10,000 (brain)
Naltrexone	Opioid receptor antagonist		δ: 26.6 κ: 1.75 μ: 0.39							
Paroxetine	Selective serotonin reuptake inhibitor	>10,000 (brain)		108 (brain)	α1: 1,868 (cortex) α2: 3,915 (cortex)	242	963	>10,000 (brain)	0.58	1A : >10,000 (brain) 2 : >10,000 (brain)
Fluvoxamine	Selective serotonin reuptake inhibitor			>10,000	α1: 1,288 (cortex)	2,931	>10,000		12.5	

Ki values mean the binding affinities of drugs to receptors and transporters for various neurotransmitters. Ki values used in this plot were adopted from PDSP Ki data base (http://pdsp.med.unc.edu/pdsp.php).
( ) means the source of receptor or transporter. Only the Ki values obtained using human source were identified.

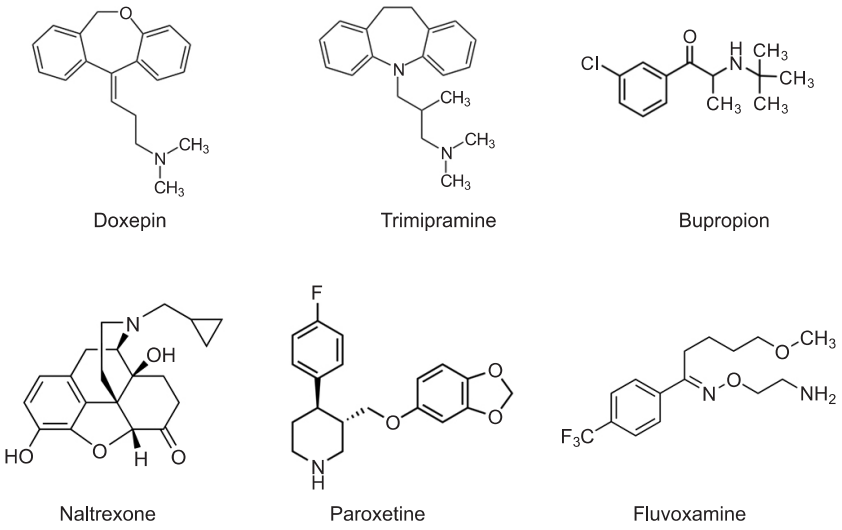

Fig. 1. Chemical structures of psychotropic drugs with antipruritic effects in patients of atopic dermatitis.

pressant acting via inhibition of both noradrenaline and dopamine reuptake. Case reports have shown that patients with AD can have symptomatic improvement with oral bupropion treatment (Gonzalez *et al.*, 2006). Fig. 1 summarizes the Ki values of antipruritic psychotropic drugs to various receptors or transporters for neuromediators.

In addition, psychotropic drugs that act on 5-HT receptor or serotonin transporter (SERT) showed antipruritic effects in AD. An anxiolytic 5-HT agonist for 5-HT1A receptor, tandospirone citrate showed a significant improvement in SCORAD (SCORing Atopic Dermatitis) indices (Kawana *et al.*, 2010). The selective serotonin reuptake inhibitor (SSRI) paroxetine and fluvoxamine considerably reduced pruritus in patients with AD in an open label two-armed proof of concept study (Diehn and Tefferi, 2001; Ständer *et al.*, 2009). Yaris *et al.* and Zylicz *et al.* suggested that antipruritic effect of paroxetine might be predominantly due to its central action rather than peripheral effects (Yaris *et al.*, 2003; Zylicz *et al.*, 2003). However, considering the reports that intradermal administration of 5-HT could induce pruritus (Yamaguchi *et al.*, 1999) and that selective 5-HT1A receptor agonist, tandospirone citrate inhibited stress-enhanced degranulation of skin mast cells (Shimoda *et al.*, 2010), further studies should be conducted to elucidate whether the antipruritic effects of these serotonergic drugs are due to the central sedative effect based on their additive antihistaminic or anticholinergic action or peripheral effect. 5-HT is one of the key neurotransmitter that acts in both central and peripheral nervous system (Slominski *et al.*, 2005). Dysregulation of 5-HT leads to sleep disorder, anxiety, depression, and aggressiveness. *In vitro* results show that 5-HT exerts variable effects on skin cells (Slominski *et al.*, 2003). It stimulates growth of dermal fibroblasts in a dose-dependent manner (Seuwen and Pouyssegur, 1990). Immortalized epidermal melanocytes exhibit serotonin-stimulated growth when the cells had been cultured without melanocyte growth supplements (Slominski *et al.*, 2003). In addition, recent reports showed that 5-HT induces melanogenesis via 5-HT receptor 2A(5-HT2A)(Lee *et al.*, 2011).

In skin, 5-HT is involved in vasodilaion, inflammation, immunomodulation and pruritogenic effects via interaction with membrane-bound receptors, which are categorized into 7 families (5-HT1-7) with at least 21 subtypes (Mössner and Lesch, 1998; Kroeze *et al.*, 2002; Slominski *et al.*, 2003).

SERT determines the magnitude and duration of the serotonergic response via recycling released 5-HT in the synaptic cleft. Because SERT can terminate the action of 5-HT on nerve, the SSRIs targeting SERT have been used as antidepressants and anxiolytics.

However, 5-HT receptors and SERT are not confined to nerves. 5-HT receptors were found to be expressed on lymphocytes, dendritic cells and macrophages (Meredith *et al.*, 2005). Expression of SERT on human blood lymphocytes (Faraj *et al.*, 1994), murine peritoneal macrophages and dendritic cells (Rudd *et al.*, 2005) has been reported.

In human skin, Slominski *et al.* reported an expression of the serotonergic receptors on human keratinocytes, melanocytes and dermal fibroblasts (Slominski *et al.*, 2003). 5-HT1A receptors were found on mast cells and melanocyte-like cells, 5-HT2A receptors and SERT on lymphocytes, NK cells and langerhans cells (LCs) in the eczematous skin of patients suffering allergic contact dermatitis (El-Nour *et al.*, 2007). Pharmacological studies indicate that 5-HT3 receptors are also expressed on sensory nerve endings (Weisshaar *et al.*, 1997). $CD3^+$ cells in skin co-expressed 5-HT2A and SERT (El-Nour *et al.*, 2007). Moreover, skin mast cells showed increased expression of serotonin receptor 5-HT1A, 5-HT2A, SERT in lesional skin of patients with stress-associated AD, compared with non-lesional skin (Lonne-Rahm *et al.*, 2008). Fig. 2 summarizes the reports about the role of serotonin in neuroimmunologicalinteraction in skin of atopic dermatitis patients.

A recent paper suggested a possible association between polymorphisms in the SERT gene and aggravation of AD. Among the three known polymorphisms affecting transcription of SERT gene, a tendency towards high prevalence of the short (10-copy) variant of STin2 was found in AD patients. All AD patients with high-anxiety traits carried the short variant of STin2. In the corresponding healthy control group, the prevalences of the 10-and 12-copy variants were 62% and 38%, respectively (p<0.01) (de Mel *et al.*, 2012). Interestingly, 5-HT is also reported to modulate T-cell activation and differentiation

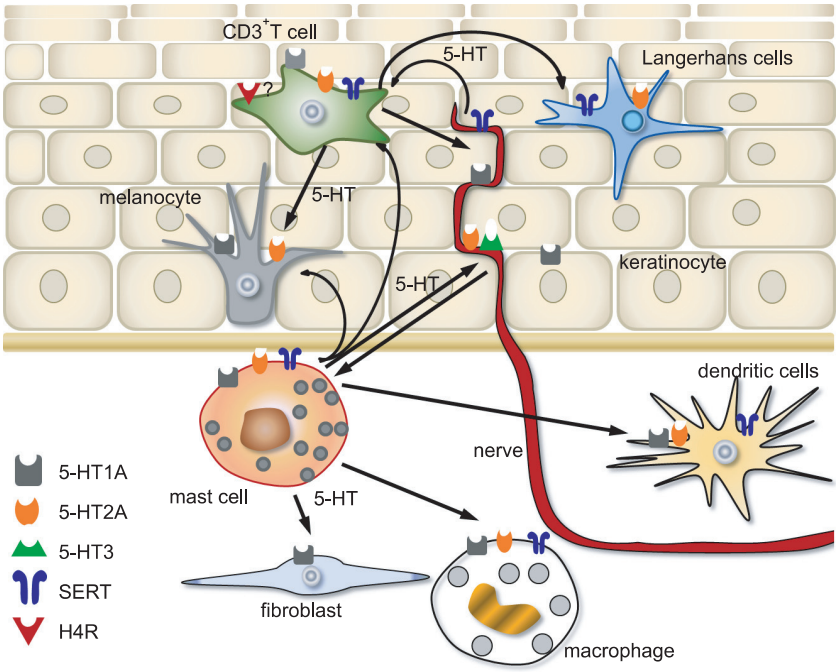

Fig. 2. Graphic summary about the role of serotonin in neuroimmunological interaction in skin of atopic dermatitis patients.

strongly suggesting 5-HT as one of key mediators in signalling between nervous system and immune system (Aune *et al.*, 1993; Aune *et al.*, 1994; Gordon and Barnes, 2003). Thus it is not surprising that serotonergic drugs showed modulating effect on cells of the immune system (Frank *et al.*, 1999; Pellegrino and Bayer, 2000). Release of 5-HT by fenfluramine treatment has been shown to decrease whole blood lymphocyte proliferation in rats (Connor *et al.*, 2000). In addition, a SSRI fluoxetine and 5-HT2 receptor agonist 2, 5-dimethoxy-4-iodoamphetamine (DOI) administration resulted in a significant decrease in concanavalin A-induced lymphocyte proliferation (Pellegrino and Bayer, 2002). Pellegrino *et al.* suggested the effects of fluoxetine on lymphocyte proliferation were the result of elevated central serotonin neurotransmission and activation of central 5-HT2 receptors, because pretreatment with the 5-HT2 antagonist ritanserin or ketanserin almost completely antagonized the decrease in lymphocyte proliferation by fluoxetine (Pellegrino and Bayer, 2002). On the other hand, a couple of reports showed that fluoxetine promoted the Ca^{2+}-mediated proteolysis of protein kinase C and increased cyclic AMP levels, impairing proliferation of human peripheral blood T cells, when optimal mitogenic stimuli was used (Edgar *et al.*, 1999). $CD3^+$ cells in skin co-expressed 5-HT2A and SERT (El-Nour *et al.*, 2007). Thus the question whether the cyclic AMP-mediated suppression of T cell proliferations by fluoxetine might work in skin T cells and by other SSRI needs further study.

Considering all these results and the critical roles of skin T cells in the pathophysiology of AD, the antipruritic effects of SSRIs in AD patients might be due to their suppressive effect on T cells at least partly. However, it is still unclear whether the antipruritic effects of neuromodulators are mediated directly via suppression of lymphocyte function or indirectly by the modulation of neuro-immune interaction.

SUMMARY

Controlling and management of prurirtus still remains as unmet needs mainly due to the distinctive multifactorial pathogenesis of pruritus in AD. Based on the distinct feature of AD that psychological state of patients substantially influence the intensity of pruritus, various psychotropic drugs have been used in clinic to relieve pruritus of AD patients. Only several psychotropic drugs including SSRI were reported to show real antipruritic effects in AD patients and the precise mechanisms of antipruritic effect of these drugs are still unclear. Interestingly, drugs that increased 5-HT concentration showed significant decrease in lymphocyte proliferation, suggesting that antipruritic effects of SSRIs in AD patients might at least partly due to their suppressive effect on T cells considering the critical roles of skin T cells in the pathophysiology of atopic dermatitis. However, further studies should be conducted to elucidate the precise mechanism of neuro-immune interaction in pruritus of AD.

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