表1 結果

		n = (男/女)	年齢 (平均±SD)	Skindex-16 (平均±SD)				DLQI (平均±SD)						
				症状	感情	機能	総合	症状感情	日常活動	レジャー	仕事学校	人間関係	治療	総合
全体		2,643	45±18	34±31	55±33	21±26	39±26	2.2±1.8	1.2±1.7	0.9±1.6	0.6±1.0	0.3±1.0	0.4±0.7	5.6±6.1
性別	男	1,197	47±19	32±31	51±32	20±26	37±26	2.1±1.7	1.0±1.6	0.9±1.6	0.6±1.0	0.4±1.0	0.3±0.7	5.3±6.2
	女	1,446	43±18	34±31	59±33	21±26	41±26	2.3±1.8	1.3±1.8	0.9±1.6	0.6±1.0	0.3±0.9	0.4±0.8	5.8±6.1
年代別	16～29歳	720(292/428)	24±3	38±31	63±31	24±27	45±25	2.5±1.8	1.4±1.8	1.0±1.6	0.7±1.1	0.4±1.0	0.4±0.8	6.5±6.3
	30～49歳	866(359/507)	38±6	36±31	57±33	23±28	41±27	2.3±1.8	1.3±1.7	1.0±1.6	0.6±1.0	0.4±1.0	0.4±0.8	6.0±6.3
	50～69歳	768(393/375)	59±6	28±29	50±32	17±23	34±25	1.8±1.6	0.9±1.5	0.9±1.6	0.5±0.9	0.3±0.9	0.3±0.7	4.6±5.8
	70歳～	289(153/136)	77±5	29±31	47±33	17±23	33±26	1.8±1.6	1.0±1.6	0.7±1.5	0.4±0.9	0.3±1.0	0.3±0.7	4.4±5.9
疾患群	湿疹群	740(340/400)	41±18	52±29	71±26	29±27	53±23	3.2±1.7	1.7±1.8	1.3±1.7	0.8±1.1	0.5±1.1	0.5±0.9	8.0±6.4
	腫瘍群	688(306/382)	49±19	15±22	35±29	7±15	21±20	1.0±1.3	0.4±1.0	0.3±0.9	0.2±0.6	0.1±0.5	0.1±0.3	2.1±3.6
	感染症群	297(171/126)	46±17	34±30	50±32	17±22	36±24	2.0±1.5	1.1±1.7	1.0±1.7	0.7±1.1	0.5±1.2	0.3±0.7	5.5±6.2
AD	AD	224(98/126)	28±7	66±25	80±21	41±28	64±20	4.0±1.6	2.5±2.0	1.8±2.0	1.2±1.1	0.7±1.3	0.8±1.1	10.9±7.2
	AD(男)	98	28±8	67±25	78±22	43±29	64±22	3.9±1.6	2.4±2.1	2.1±2.2	1.3±1.2	0.8±1.3	1.0±1.1	11.5±7.8
	AD(女)	126	28±7	64±25	82±20	39±26	64±19	4.0±1.6	2.5±1.9	1.6±1.8	1.1±1.1	0.6±1.3	0.7±1.0	10.5±6.6
	AD10代	18(9/9)	18±1	67±21	79±22	31±26	61±20	3.7±1.4	2.4±2.0	1.7±1.7	1.2±1.2	0.3±0.8	0.6±1.1	9.9±6.6
	AD20代	126(56/70)	24±3	65±24	82±18	39±26	65±18	4.0±1.5	2.4±2.0	1.7±2.0	1.2±1.2	0.6±1.2	0.8±1.0	10.6±7.0
	AD30代	64(25/39)	33±2	65±27	78±23	44±29	64±23	4.0±1.7	2.6±1.9	1.8±1.8	1.1±1.1	0.8±1.3	0.9±1.1	11.2±6.9
	AD40歳～	16(8/8)	46±5	70±31	76±28	49±34	66±28	4.1±2.0	2.7±2.3	2.8±2.4	1.3±1.2	1.4±1.8	1.1±1.4	13.3±9.3
疾患	蕁麻疹	95(39/56)	38±15	42±23	67±24	26±24	48±19	2.9±1.4	1.5±1.8	1.1±1.4	1.3±1.2	0.3±0.7	0.4±0.6	7.6±5.5
	乾癬	65(43/22)	47±18	34±27	76±24	32±30	52±22	3.0±1.9	1.4±1.4	0.9±1.5	0.4±0.6	0.5±1.3	0.7±0.9	6.9±5.5
	痤瘡	62(21/41)	28±8	38±30	83±23	36±34	57±22	3.0±1.7	1.4±1.8	1.1±1.6	0.8±1.1	0.6±1.2	0.7±1.0	7.5±6.5
	脱毛	67(26/41)	37±14	15±20	71±25	31±32	44±20	2.4±1.5	1.6±1.9	1.1±1.6	0.5±0.9	0.2±0.6	0.3±0.7	6.2±5.4

AD ; Atopic dermatitis

結　果

1. 患者背景

2,643例のうち男1,197例，女1,446例，最年少は16歳，最高齢は94歳，平均年齢±SDは45±18歳（男47±19, 女43±18）であった（表1）．年齢分布は20代が25%，続いて30代20%，50代16%の順であった．

それぞれの主病名を疾患群に分類したところアトピー性皮膚炎を含む湿疹皮膚炎群が28%と最も多く，続いて腫瘍群27%，感染症群11%の順であった（図1）．アトピー性皮膚炎は全体の8%，224人（男98, 女126）であり，最年少は16歳，最高齢は56歳，平均年齢±SDは28±7歳（男28±8, 女28±7）であった．

2-1. 全体の結果

Skindex-16のスコア結果は，どの尺度も最小値0，最大値100であり，平均値±SDは症状34±31，感情55±33，機能21±26，総合39±26であった．

DLQIスコア結果は，どの尺度も最小値0から，最大値は症状・感情6，日常活動6，レジャー6，仕事・学校3，人間関係6，治療3，総合30点といずれも各スコアの最高値まで分布していた．平均値±SDは症状・感情2.18±1.77，日常活動1.17±1.69，レジャー0.93±1.59，仕事・学校0.60±0.98，人間関係0.34±0.96，治療0.35±0.75，総合5.56±6.15であった．

2-2. 性　差

Skindex-16の下位尺度の平均点を男女別で比較すると，男女ともに感情，症状，機能の順にスコアが高く，また総合スコアと感情スコアでは有意に女性の平

均得点が高かった．DLQIの下位尺度の平均点を男女別で比較すると，総合スコア，症状・感情スコア，日常活動スコアで有意差をもって女性の得点が高かった(図2)．

2-3. 年代別での比較

16から29歳，30～49歳，50～69歳，70歳以降の年代別に比較するとおおむね高齢になるほど各年代のスコア平均が低値となる傾向を認めた(図3)．年齢と各スコアでSpearman's correlation testを行ったところ，すべての下位尺度でr<0.18 (P<0.05)であり，相関はみられなかった．

2-4. 疾患群での比較

症例数の多かった湿疹皮膚炎群，腫瘍群，感染症群で比較すると，Skindex-16およびDLQIのすべての尺度で湿疹皮膚炎群のスコアが最も高値で，次に感染症群が続き，腫瘍群のスコアが最も低値であった(図4)．

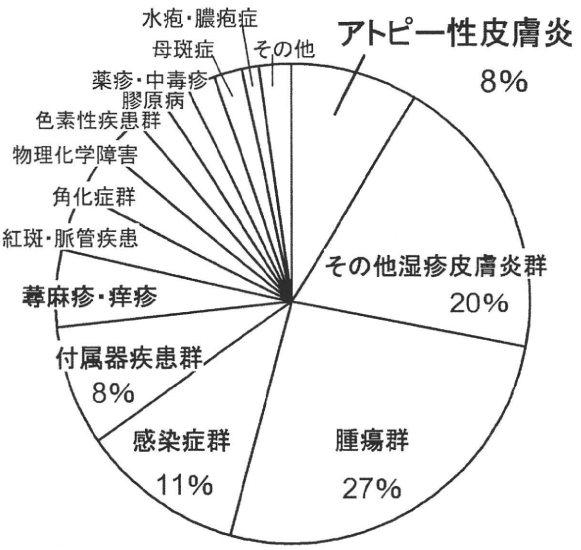

図1　患者背景

3-1. アトピー性皮膚炎患者の結果

Skindex-16のスコア結果は，感情スコアは最小値14.3，総合スコアは最小値10.4，最大値99.0であり，その他の尺度は最小値0，最大値100であった．平均値±SDは症状66±25，感情80±21，機能41±28，総合64±20であった．DLQIスコア結果は，どの尺度も最小値0から，最大値は症状・感情6，日常活動6，レジャー6，仕事・学校3，人間関係6，治療3，総合30点といずれも各スコアの最高値まで分布していた．平均値±SDは症状・感情3.96±1.60，日常活動2.46±1.97，レジャー1.81±1.95，仕事・学校1.17±1.14，人間関係0.68±1.27，治療0.85±1.07，総合10.93±7.15であった．

3-2. アトピー性皮膚炎患者での性差

アトピー性皮膚炎患者においてSkindex-16の下位尺度の平均点を男女別で比較すると，男女ともに感情，

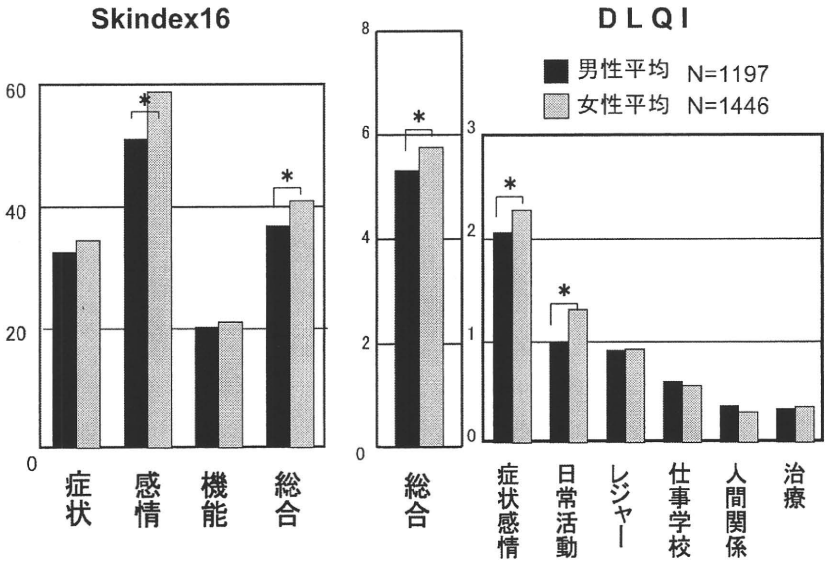

図2　全患者での性差

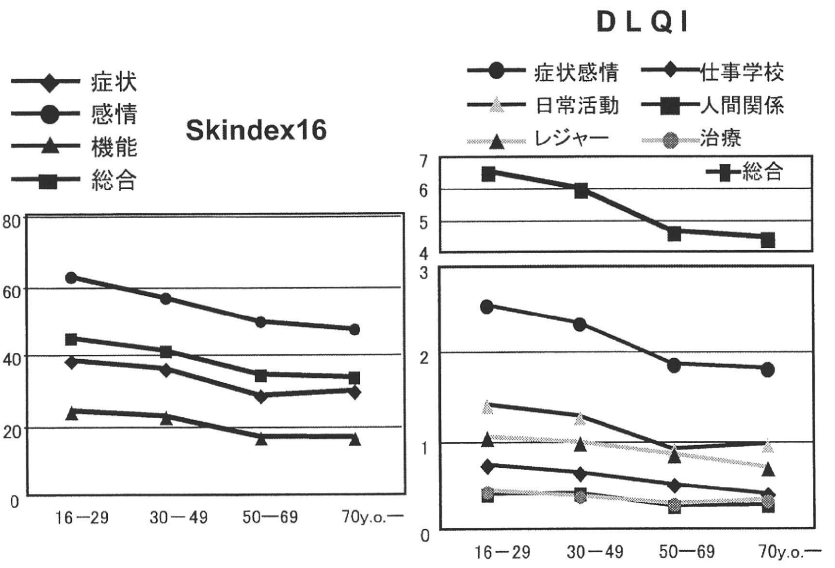

図３ 全患者の年代別比較

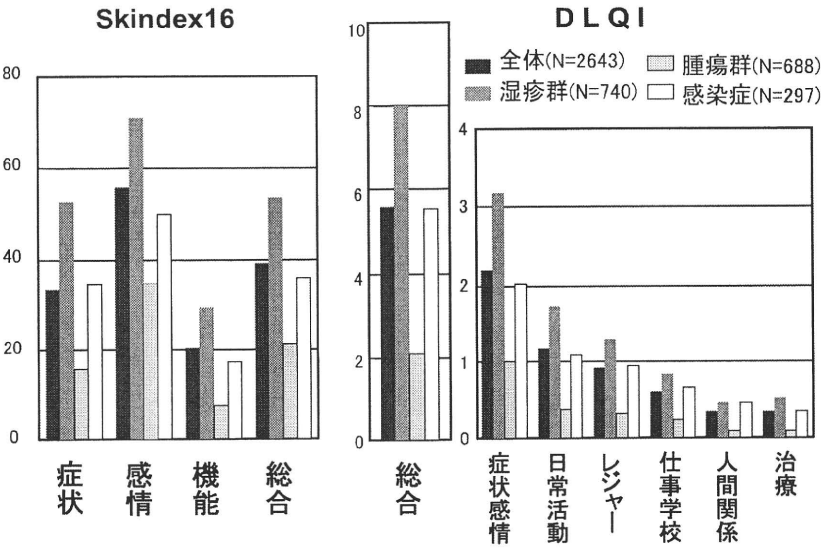

図４ 湿疹皮膚炎群，腫瘍群，感染症群の比較

症状，機能の順にスコアが高かった．いずれの下位尺度でも男女間に有意差を認めなかった．DLQI の下位尺度の平均点では，治療スコアにおいて有意に男性平均値が高値であった（図 5）．

3-3. アトピー性皮膚炎患者での年代差

アトピー性皮膚炎患者において Skindex-16 の症状スコアは 10 から 30 代，感情スコアは 20 代から 40 代以降，総合スコアは 20 代から 30 代にかけて，また DLQI の日常活動スコアは 10 から 20 代，仕事学校スコアは 20 代から 30 代にかけて減少したもの，他は加齢により各年代の平均スコアが上昇する傾向がみられた（図 6）．年齢と各スコアで Spearman's correlation test を行ったところ，各下位尺度は $r<0.20$（一部 NS）で相関は見られなかった．

3-4. アトピー性皮膚炎患者とその他湿疹群，他全患者の比較

アトピー性皮膚炎とアトピー性皮膚炎を除く湿疹皮膚炎群，及びアトピー性皮膚炎患者を除く全患者のス

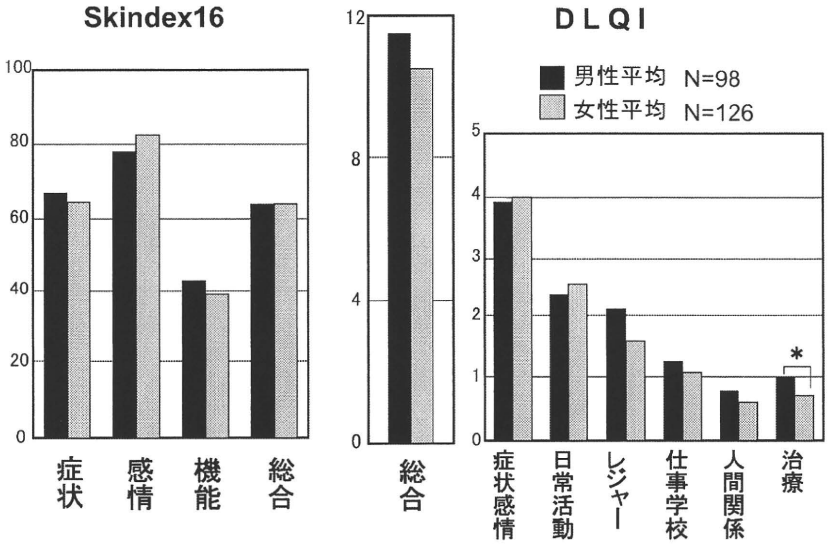

図５　アトピー性皮膚炎患者での性差

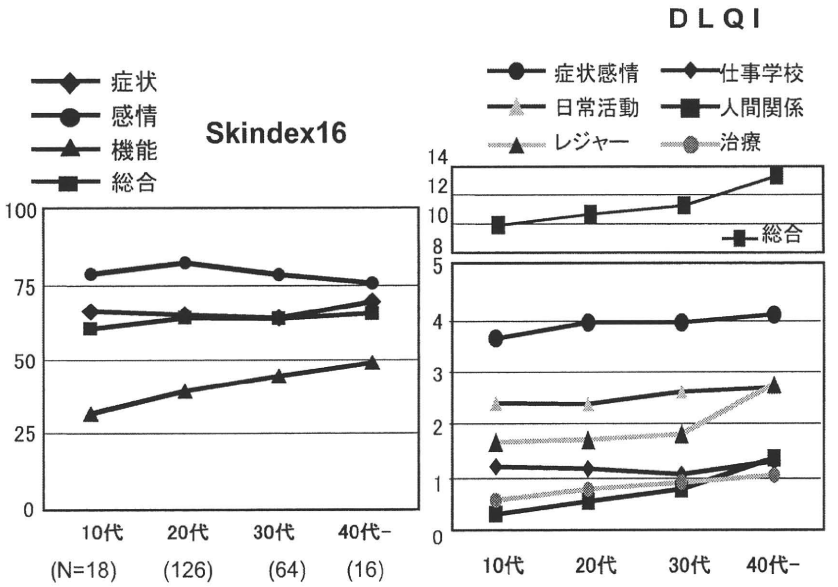

図６　アトピー性皮膚炎の年代別比較

コアを比較したところ，すべての項目で有意差をもってアトピー性皮膚炎のスコアが高値となった（図7）.

3-5. アトピー性皮膚炎患者と他の疾患患者との比較

アトピー性皮膚炎患者と蕁麻疹，乾癬，痤瘡，脱毛症患者のスコアを比較したところ，Skindex-16総合，症状スコアはアトピー性皮膚炎患者が有意に最も高値であった．感情スコアでは蕁麻疹，脱毛症患者より，機能スコアでは蕁麻疹，乾癬，脱毛症患者より，それぞれ有意にアトピー性皮膚炎患者の方が高値であった（図8）. DLQIでは総合，症状感情，日常活動，レジャースコアはアトピー性皮膚炎患者で有意に最も高値であった（図9）.

3-6. 各質問別の得点

アトピー性皮膚炎患者では，Skindex-16の各質問の平均得点をみると，かゆみや痛み，うっとうしい，見

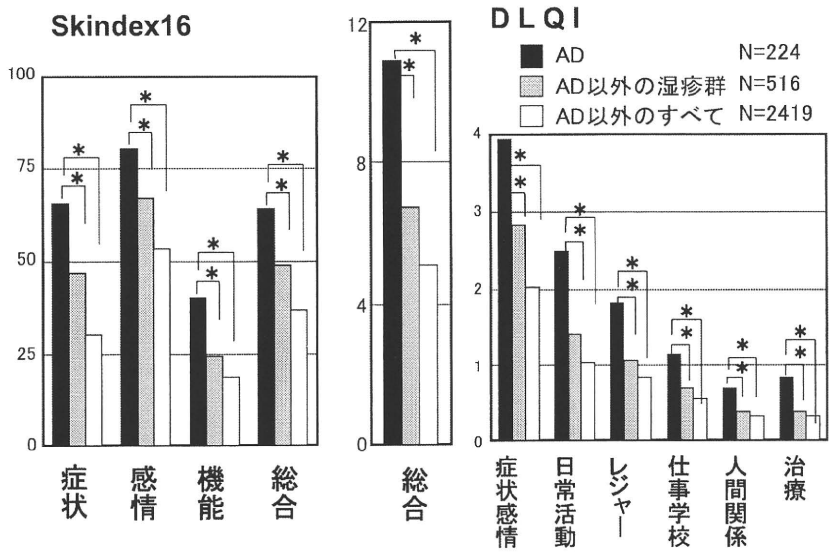

図７ アトピー性皮膚炎患者とその他湿疹群，他全患者の比較

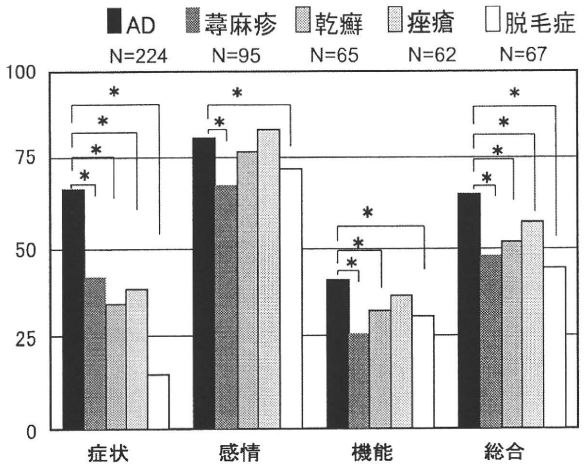

図８ アトピー性皮膚炎と他疾患の比較：Skindex-16

た目が気になる，症状が長引いたり繰り返し悪くなったりする，などの項目が高得点となった．逆に人の輪には入りづらい，愛情や好意をおもてに出すのがむずかしい，人づきあいなどの項目は低い得点であった．DLQI においてはかゆみや痛み，恥ずかしく思ったりまわりの人の目が気になる，服装に影響がある，の順に高得点であった（表 2）．

考　察

皮膚科疾患はかゆみなどの自覚症状が慢性的に続き，病変が患者自身や他者の目に触れるため，患者の QOL を損ねることが多い．特にアトピー性皮膚炎は寛解増悪を繰り返すことにより長期にわたりかゆみが存在し，顔面など露出部に皮疹の範囲が広がり外見上の問題も生じることから，患者本人及び家族の QOL にも影響が大きいと考えられる．

九州大学病院では 2007 年から初診患者に対し DLQI と Skindex-16 を用いた調査を行っている．調査を開始するにあたり，皮膚疾患特異的 QOL 調査票の中でも，reliability・validity が確認されている日本語版があり，質問項目も少なく簡便に使用できる DLQI と Skindex-16 を使用することとした．両者の比較をした大規模調査の報告はなかったため，両調査票を比較することも目的の 1 つであった．DLQI と Skindex-16 の違いについては前回報告した[9]が，今回の結果からも，特にアトピー性皮膚炎患者の QOL 調査結果は DLQI も Skindex-16 も同様の傾向がみられた．DLQI の長所としては質問項目が少なく，非営利目的であれば無料で使用することができること，英文の報告が多いことなどがあげられ，Skindex-16 では質問の内容が日本人にうけいれられやすい項目になっており，各下位尺度も比較しやすいことがあげられるため，目的にあわせてどちらかを選択して使用するのがよいと考えられる．

どちらも今回は 2007 年から 2 年分の結果を集計し，全患者とアトピー性皮膚炎患者との比較を行った．各スコア平均は疾患群により異なるが，湿疹群の各スコアは他の疾患群のスコアよりも高値であった．また，その湿疹群の中でもアトピー性皮膚炎患者のスコアが

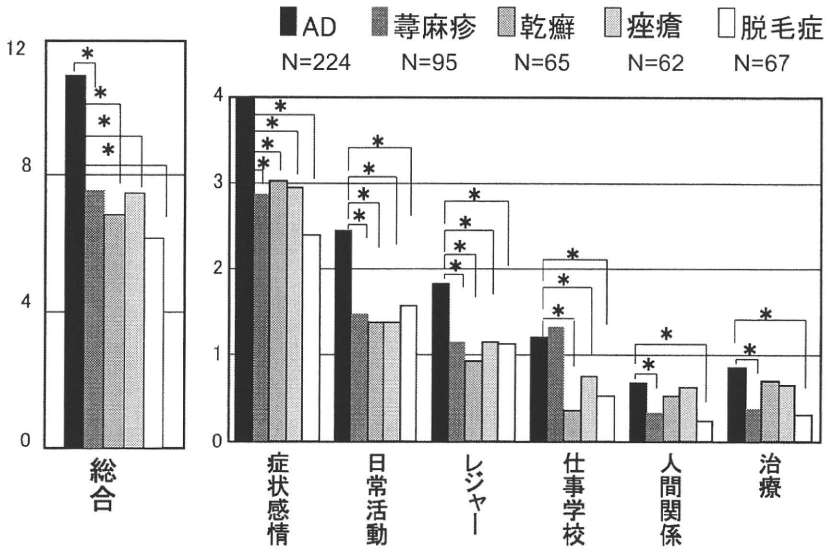

図９　アトピー性皮膚炎と他疾患の比較：DLQI

表２　各質問の平均得点

			全患者	AD
Skindex-16	Q1	かゆみや痛み	2.74	5.33
	Q2	灼熱感，刺すような感じ	1.89	3.88
	Q3	痛み	1.63	3.02
	Q4	刺激感	1.78	3.51
	Q5	症状が長引く，繰り返し悪くなる	3.26	5.23
	Q6	症状の悪化についての心配	3.87	4.92
	Q7	見た目が気になる	3.91	5.23
	Q8	いらだちや挫折感	2.84	4.54
	Q9	恥ずかしく思う	2.65	4.16
	Q10	うっとうしい	3.68	5.24
	Q11	憂うつ	3.06	4.43
	Q12	人付き合い	0.93	1.83
	Q13	人の輪に入りづらい	0.88	1.70
	Q14	愛情や好意をおもてにだしづらい	0.79	1.75
	Q15	日常生活に支障	1.93	3.71
	Q16	仕事や余暇を楽しむのが難しい	1.65	3.19
DLQI	Q1	かゆみや痛み	1.37	2.45
	Q2	恥ずかしく思う，人の目が気になる	0.81	1.50
	Q3	買い物，家事，家の仕事	0.62	1.23
	Q4	服装	0.55	1.24
	Q5	人付き合い，自由時間	0.46	0.96
	Q6	スポーツ	0.46	0.85
	Q7	仕事，勉強	0.60	1.17
	Q8	夫，妻，恋人，親しい友人，身内との関係	0.19	0.42
	Q9	性生活	0.15	0.26
	Q10	治療や手入れ	0.35	0.85

AD; Atopic dermatitis

更に高値であることから，アトピー性皮膚炎患者のQOLはとりわけ障害されているといえる．蕁麻疹，乾癬，痤瘡，脱毛患者のスコアと比較すると，総合スコアを含め多くの下位尺度で有意差をもってアトピー性皮膚炎患者のQOLが障害されている結果であった．Skindex-16の感情スコアは蕁麻疹と脱毛症のみ有意差を認め，他の疾患でも感情面ではアトピー性皮膚炎と同様にQOLが障害されると考えられた．男女比較ではSkindex-16の総合，感情，DLQIでは総合，症状感情，日常活動で女性のスコアが有意に高値であった．今回データは示していないが，湿疹皮膚炎群，腫瘍群，感染症群で男女比較してもSkindex-16の総合，感情，症状，DLQIの総合，症状感情，日常活動スコアは女性の方が高い傾向があり，女性のQOLの方が障害されやすいといえる．しかしアトピー性皮膚炎患者においては，男性が有意に高かったDLQIの治療スコアを除いて，男女の平均スコアに有意差を認めず，女性も男性もどちらのQOLも障害されると考えられた．年代別には，全患者の結果では高年代の平均スコアが低い傾向があったが，アトピー性皮膚炎患者においては10代から40代以降にかけてもスコアの改善傾向はみられず，高齢になっても引き続きQOLが障害されている結果となった．

アトピー性皮膚炎患者のQOLに関して，本邦では2004年に檜垣らがSkindex-16を用いてアトピー性皮膚炎患者162名に対して調査を行い，症状，感情，機能のいずれのスコアも良性腫瘍の患者と比較して有意に高値であり，またそのスコアとアトピー性皮膚炎の重症度には正の相関が認められたことを報告している．縦断的検討では患者自身の症状改善につれてスコアが改善することも記載されている[10]．他の大規模調査としては2007年に川島らがアトピー性皮膚炎患者771名に外用と抗ヒスタミン薬による標準的薬物療法を施行し，4週後，12週後にSkindex-16を用いて評価を行い，重症度の改善と，Skindex-16の全体およびすべての下位尺度で4週後と12週後に有意なスコアの改善がみられ，QOLも向上したことを報告している[11]．DLQIを用いた本邦での大規模調査は検索しえなかったが，Skindex-16と同様に治療の効果判定のために使用されることがあり，治療による重症度スコアの改善とDLQIのスコアの改善が関連していることが報告されている[12]．海外の研究ではDLQIが用いられることが多く，健常人と比較してアトピー性皮膚炎患者のQOLは低下していることや，アトピー性皮膚炎の重症度とDLQIスコアが相関すること[13)~15)]，SF-36など他の調査票結果との相関などを論じているものが多い[16)]．他の皮膚疾患との比較では，アトピー性皮膚炎患者と乾癬患者のQOLは他の皮膚疾患患者よりも低下しているとの報告[17)]や，乾癬とアトピー性皮膚炎の比較では366名の調査でQOLに差がなかったとの報告もある[18)]．またアトピー性皮膚炎患者のDLQI結果における性差[13) 16)~19)]や，DLQIスコアと年齢に相関はなかった[13) 14)]との報告があるが，症例数は32人[13)]から239人[19)]と少なく，アトピー性皮膚炎の患者QOLへの影響はいまだ十分な検討が行われているとは言い難い．

今回の調査の限界については，アトピー性皮膚炎患者についての症例数が少ないこと，また大学病院外来を初診にて受診し，かつ調査票に記入してもらえた症例のみ集計しているため，母集団に偏りがあることが挙げられる．大学病院を受診する患者は市中病院と比較し，より重症であったり，軽症であっても疾患について悩みQOLが障害されている症例が多いと考えられる．今回の検討でアトピー性皮膚炎患者は，他疾患(群)患者に較べ，QOLがより強く障害される傾向があると考えられた．QOLが低下する疾患はより長い診療時間や多くの治療法が必要とされると考えられる．アトピー性皮膚炎は多くの病院等の施設でアトピー性皮膚炎外来など特殊外来を設置していることが多いが，今回のQOL調査結果は特殊外来の必要性の根拠の1つと考えられ，今後QOLの低い患者は診療内科との協力を考えるなどさらなる治療方針が必要となってくるかもしれない．今回は縦断的な調査は行っていないが，皮膚状態の改善を自覚していない患者に経時的にQOL調査を行うことによって，QOLの改善を治療効果の1つとして患者自身に示すことも可能である．性差，年代差による比較でも，アトピー性皮膚炎患者は，他疾患群患者と異なるQOLの障害パターンを示した．今後症例数を増やしアトピー性皮膚炎の重症度や罹患期間などの情報を加えて，さらに詳細な検討を行う必要があると考えられる．

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Using the Japanese Version of Skindex-16 and DLQI to Measure the QOL of New Outpatients with Atopic Dermatitis

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(Received February 24, 2009; accepted for publication May 21, 2009)

We used the Japanese version of Skindex-16 and DLQI to assess the quality of life (QOL) of 224 patients with atopic dermatitis (AD) among 2,643 new Japanese outpatients who visited the Department of Dermatology, Kyushu University Hospital from January 2007 to December 2008, We found that the QOL of AD patients was more severely impaired than that of patients with other skin diseases. There were no differences in QOL between male and female AD patients; however, the women had a worse QOL compared to men with other conditions. In addition, the QOL of AD patients was impaired irrespective of age, whereas younger patients with other illnesses tended to have a poorer QOL than older ones.

(Jpn J Dermatol 120: 45～54, 2010)
Key words: atopic dermatitis, quality of life, DLQI, Skindex-16, dermatology

EXPERT REVIEWS

Recent advances in pathophysiological mechanisms of itch

Expert Rev. Dermatol. 5(2), 197–212 (2010)

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Itch (or pruritus) is an unpleasant sensation inducing a desire to scratch. As part of the body's defense mechanism, itch guards the skin against potentially dangerous organisms or stimuli. Moreover, itch is a major and distressing symptom of many skin and systemic diseases. Histamine is the best known pruritogen in humans, and is also regarded as an experimental itch-causing substance. Clinically, antihistamines – that is, H_1-receptor blockers – are commonly used for all types of itch resulting from renal and liver diseases, as well as from serious skin diseases, such as atopic dermatitis. However, antihistamines often lack efficacy in patients with chronic itch, as there are many other itch-causing substances, such as proteases, neuropeptides, cytokines and opioids, and their cognate receptors, such as thermoreceptors, PAR-2 and opioid receptors. Recently, potential roles of new histamine receptors in pruritus have also been identified. Itch is transmitted to the CNS by specialized nerve fibers and sensory receptors. Recent studies regarding gastrin-releasing peptide receptors indicated that itch and pain have their own neuronal pathways. As a cutaneous sensory perception, itch may require excitation of neuropeptide-containing free nerve endings of unmyelinated C-fibers, such as gastrin-releasing peptide+ fibers. In addition, neuronal sensitization caused by activation of itch-related receptors on sensory nerve fibers and increases in the number of these fibers, as well as neurogenic inflammation, are partly involved in chronic itch. This review highlights recent knowledge regarding different mechanisms that may be involved in the regulation of itch.

KEYWORDS: GRP/GRPR • histamine receptor • IL-31 • NGF • opioid system • pruritogen • Sema3A • sensory nerve fiber • skin barrier

Proposed pathophysiological mechanisms of itch

Histamine is the best known itch mediator in humans, and it is also the most commonly used experimental itch-causing substance. Antihistamines – that is, H_1-receptor blockers – frequently fail to relieve chronic itch in patients with renal failure (e.g., uremia and hemodialysis), cholestatic liver diseases and, less commonly, those with cirrhosis of diverse etiologies, cholestatic jaundice, prurigo nodularis, psoriasis, lichen amyloidosis, atopic dermatitis and others [1–4]. The lack of response to high-potency antihistamines of different types in patients with chronic itch suggests that other mediators are involved.

Potential roles of histamine receptors in itch

Histamine H_4R

Histamine, a mediator of itch in normal human skin, has been shown to induce increased itch responses in the lesional skin of patients with atopic dermatitis compared with normal skin [3]. Similar responses to histamine, measured as increases in scratching behavior, have been reported in rodents and primates, suggesting an evolutionarily conserved pathway.

Increased histamine levels have been noted in the skin and plasma of patients with atopic dermatitis [5,6] and chronic urticaria [7]. Histamine levels are also increased in psoriatic skin [8]. For all these conditions, traditional antihistamines are generally regarded as ineffective.

It is now known that the diverse biological effects of histamine are mediated through four different histamine receptors. H_4R, the most recently identified histamine receptor, has been shown to be closely related to histamine-mediated itch in animal models [9–11]. Specific H_4R agonists were shown to induce itch, whereas pretreatment with H_4R antagonists blocked these responses [10]. Similarly, histamine or H_4R

 10.1586/EDM.10.7 ISSN 1746-9872

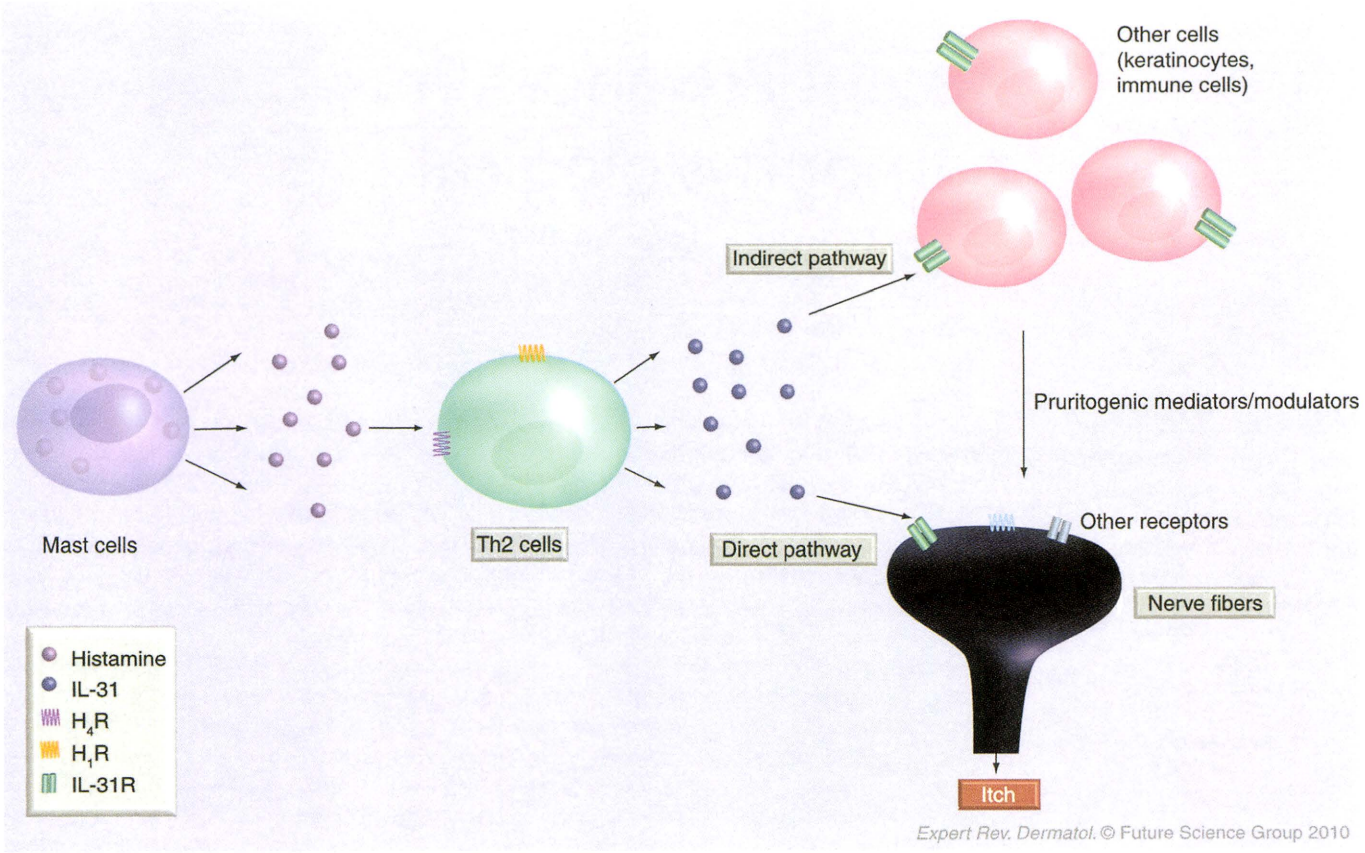

Figure 1. Itch pathway via histamine H_4R in Th2 cells. Histamine released from mast cells binds H_4R on Th2 cells, thereby increasing the production of IL-31 by Th2 cells. IL-31 may elicit itch via a direct or indirect pathway.

agonist-induced itch was markedly attenuated in H_4R-deficient animals [10]. H_4R antagonists were also effective in reducing C48/80-induced itch or itch caused by IgE-mediated mast cell activation. The responses were similarly attenuated in H_4R-deficient mice. Interestingly, additional benefits were observed by inhibiting both H_1 and H_4 receptors, since inhibition of both was found to completely eliminate histamine-induced scratching.

Using mast cell-deficient mice, H_4R-mediated itch responses were shown to be mast cell-independent [10], suggesting that the peripheral role of H_4R in itch is via its expression on other dermal cells or afferent nerves. Functional H_4R has been reported to be expressed on human Th2 cells [12]. Th2 cells were found to express higher levels of H_4R mRNA and protein than Th1 cells and naive T cells, with the expression of H_4R upregulated by IL-4. H_4R agonists, in turn, upregulated the expression of IL-31 mRNA in peripheral blood mononuclear cells and Th2 cells [12]. IL-31, a novel cytokine, has been associated with Th2 cells and the induction of pruritus. This cytokine is upregulated in skin lesions of patients with atopic dermatitis, contact dermatitis and prurigo nodularis, but not in patients with psoriasis [13–15]. Similar findings have been reported in the skin of NC/Nga mice, a murine model of atopic dermatitis [16,17]. More recently, anti-IL-31 antibodies were found to ameliorate the scratching behavior in NC/Nga mice [18], suggesting that anti-IL-31 antibodies may be a therapeutic approach in the treatment of pruritus in patients with atopic dermatitis and other pruritic diseases. Thus, histamine acts on the H_4R of Th2 cells, thereby inducing an IL-31-mediated pathway for itch in the inflamed skin (Figure 1).

Histamine H_3R

A number of studies have shown that H_3R is present in various peripheral tissues [19–21]. In the periphery, it has been suggested that the H_3R exists in perivascular nerve terminals and regulates the release of histamine [19], acetylcholine [20] and noradrenaline [22]. Moreover, it has been demonstrated that histamine regulates substance P (SP) release from peripheral ending sensory nerves via H_3R [21,23], concomitant with the existence of H_3R on C-fibers [19,21]. These findings suggest that H_3R may be involved in pruritus of the skin.

A recent study demonstrated that intradermal injection of H_3R antagonists (thioperamide and AQ0145) elicited scratching behavior in ICR or mast cell-deficient mice [24]. Meanwhile, H_3R agonist ([R]-α-methylhistamine) suppressed the antagonist-induced scratching behavior in ICR mice without sedative action [24]. These observations suggest the involvement of H_3R in modulation of pruritus in the skin, and mast cells are not essential for this response. Therefore, H_3R agonists may be useful as novel therapeutic agents against pruritus. However, similar to H_4R, the roles of H_3R in human pruritic diseases remain to be elucidated.

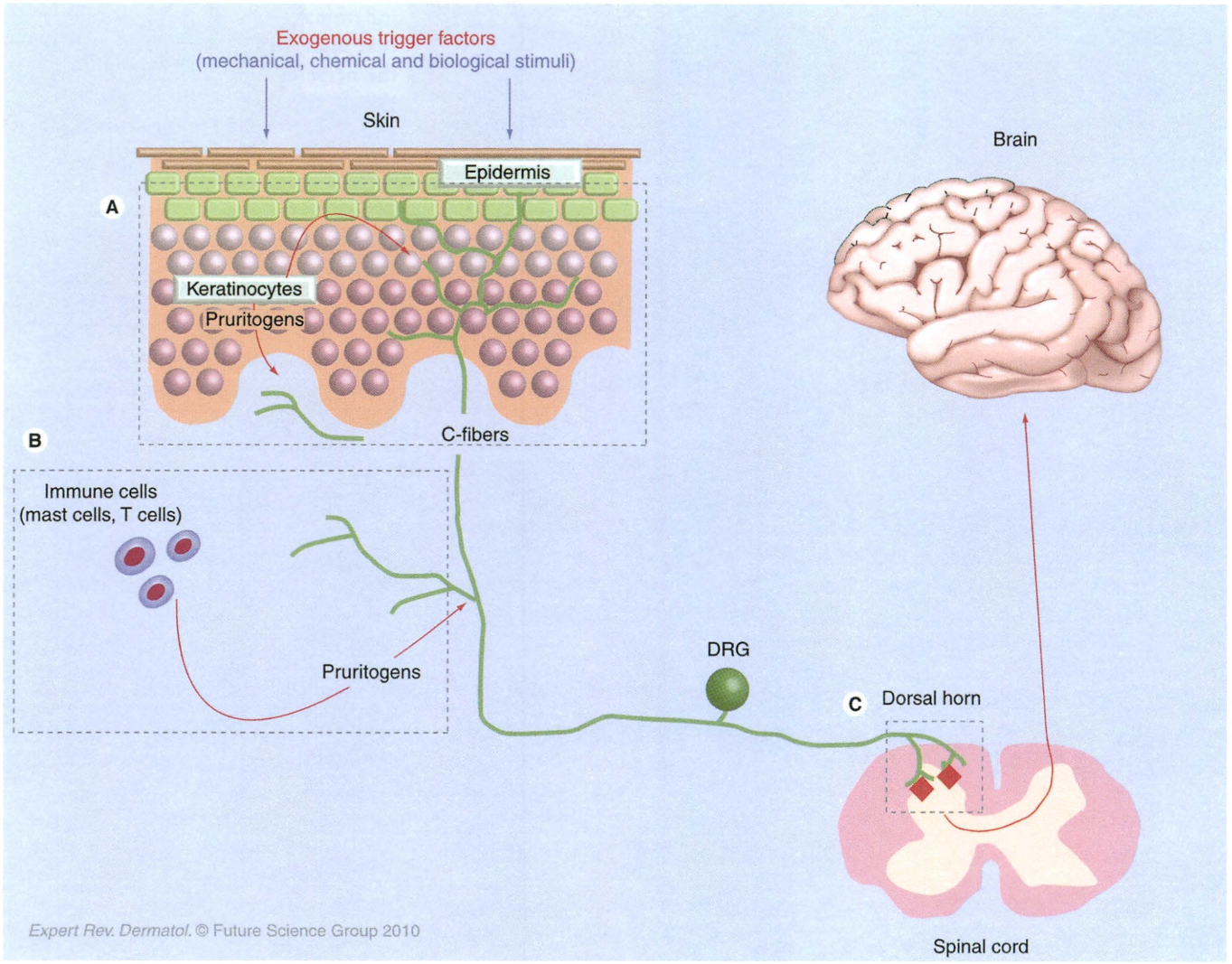

Figure 2. Interactions between pruritogen-producing cells and nerve fibers in the skin. (A) Interactions between epidermal keratinocytes and sensory nerves in the epidermis and dermis. **(B)** Interactions between immune cells (e.g., mast cells and T cells) and sensory nerves in the skin. **(C)** Pruritogenic mediators and modulators act directly or indirectly on itch-sensitive C-fibers, exciting these fibers. Itch-specific mediators (e.g., GRP) may be released by excited C-fibers to the dorsal horn, resulting in the transmission of electrical signals to the brain that are recognized as itch sensation.
DRG: Dorsal root ganglion; GRP: Gastrin-releasing peptide.

Participation of pruritogenic mediators & modulators other than histamine

A histamine-independent pathway for itch has been identified in human and animal experiments [3,4]. Endogenous mediators and modulators of pruritus in the skin include amines, proteases, neuropeptides, cytokines, opioids and cannabinoids. These molecules are involved in the pathophysiology of itch response through their interactions with immune cells, keratinocytes and nerve fibers [1] (Figure 2).

Cytokines, TNF-α & IFN-γ

IL-1

IL-1, a proinflammatory cytokine, does not seem to be correlated with itching [1]. However, a recent study suggested that IL-1β contributes to nerve regeneration by promoting neurite outgrowth following nerve injury [25]. Generally, IL-1β induces inflammation. Therefore, in inflammatory skin diseases, it may modulate itch involving the skin nerve density.

IL-2

Clinical observations suggested a role of IL-2 as an inducer of pruritus. High doses of recombinant IL-2, as administered in cancer patients, also frequently provoke flush, vasodilatation and pruritus [26]. Whether this is a direct receptor-mediated process or an indirect process – for example, via mast cells or endothelial cells – is still unknown. Intracutaneous injection of IL-2 induces low-intensity intermittent local itch accompanied by erythema in both atopic dermatitis patients and healthy controls [27,28]. Atopic dermatitis patients treated with oral cyclosporine A, a drug that inhibits the production of various cytokines including

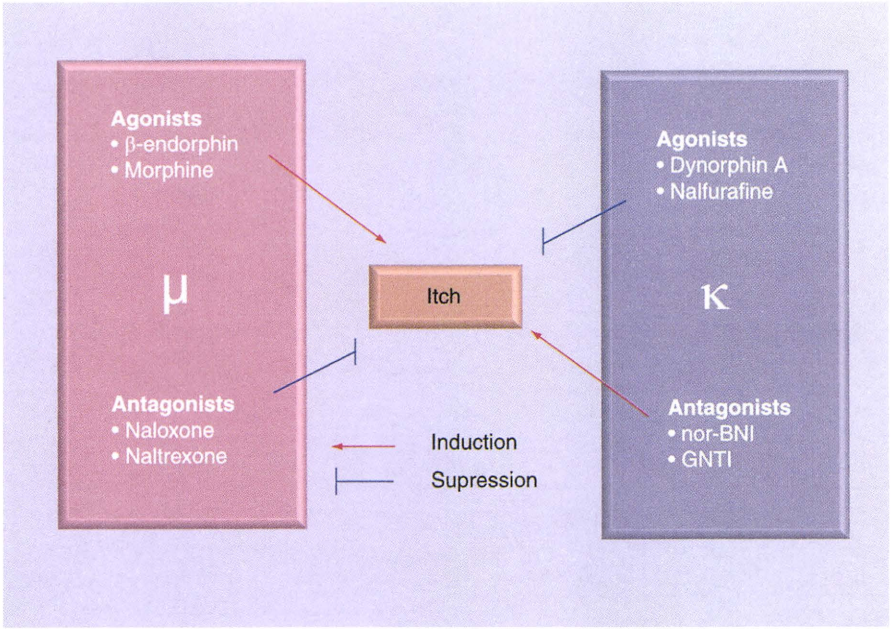

Figure 3. Proposed mechanism by which opioid systems control itch. Itch is induced by μ-agonists or κ-antagonists and suppressed by μ-antagonists or κ-agonists. GNTI: 5′-guanidinonaltrindole; nor-BNI: Nor-binaltorphimine.

IL-2, attenuated the itch [29,30]. Accordingly, systemic or topical immunosuppressants may be an effective antipruritic therapy of atopic dermatitis patients.

IL-8

Recent observations suggested a possible role of IL-8 as a mediator of itch in patients with atopic dermatitis. Several studies indicated increased levels of IL-8 in lesional skin, plasma and blood mononuclear cells, especially eosinophils of atopic dermatitis patients [31–35]. However, the capacity of IL-8 to induce pruritus is questionable, as prick testing with IL-8 does not induce whealing or pruritus [34]. Further studies are needed to clarify the influence of IL-8 on the pathophysiology of itch.

IL-31

As described above, IL-31 is produced by Th2 cells, which induces both severe pruritis and dermatitis in mice [36]. IL-31 signals are transduced via a heterodimeric receptor composed of IL-31 receptor α (IL-31Rα) and the oncostatin M receptor. Whether IL-31 exerts its effects via direct activation of the IL-31 receptors on sensory nerves [13] or indirectly, for example, via keratinocytes [37], is unknown. These findings suggest that IL-31 may induce pruritus through the induction of an as yet unknown keratinocyte-derived mediator, which subsequently activates C-fibers in the inflamed skin. IL-31 is also upregulated in pruritic, but not in nonpruritic forms of chronic skin inflammation [13,15]. Thus, IL-31 and its signaling pathway represent a novel target for antipruritic therapy.

TNF-α

TNF-α is a pivotal proinflammatory cytokine of the innate immune response and a key molecule involved in skin inflammation. One study demonstrated that mast cell-derived TNF-α is one of the nerve elongation factors in inflamed skin [38] (see section entitled 'Nerve elongation factors'). Thus, TNF-α may be a useful antipruritic target in pruritus involving skin innervation.

IFN-γ

IFN-γ is also an important mediator of skin inflammation. In previous studies, beneficial effects of IFN-γ on itch responses were clearly demonstrated in patients with atopic dermatitis [39] or in probiotic-treated atopic mice [40]. However, the mode of action and the receptor density of IFN receptors on sensory nerves in the skin remain unknown.

Protease-activated receptor 2

Protease-activated receptor 2 (PAR-2), which belongs to a subfamily of G-protein-coupled receptors, is activated by tryptase, trypsins and kallikreins, and may be activated by exogenous proteinases from bacteria, mites and plants. PAR-2 is widely distributed throughout the body, where its activation has been implicated in numerous inflammatory processes [41,42]. PAR-2 has been shown to regulate cutaneous inflammation via a neurogenic mechanism [43]. Proteases elicit itch when administered to the skin; some proteases such as tryptase act on the PAR-2 to produce itch [44]. Tryptase has been found in almost all human mast cells [45] and is an important activator of PAR-2 [46]. The expression of both tryptase and PAR-2 was found to be markedly enhanced on primary afferent nerve fibers of lesional skin in patients with atopic dermatitis compared with in normal individuals, suggesting that tryptase may be an important mediator of itch in atopic dermatitis [43]. More recently, intradermal injection of the PAR-2-activating peptide SLIGRL-NH2, but not of other PAR-activating peptides, was found to elicit scratching in healthy NC/jic mice [47]. Intravenous injection of anti-PAR-2 antibody suppressed spontaneous scratching by NC/jic mice with atopic dermatitis [47], providing further evidence that the tryptase-PAR-2 system plays a key role in pruritus during neurogenic inflammation.

Protease-activated receptor 2 is highly expressed in the epidermal keratinocytes of healthy humans and patients with atopic dermatitis, suggesting that epidermal keratinocytes are major targets of PAR-2-acting proteases [48]. Keratinocytes also release several mediators and modulators of itch [49–51]. Therefore, PAR-2-acting proteases may induce and/or modulate itch through its interaction with keratinocytes.

Recently, functional PAR-2 was found to be expressed by cutaneous human primary skin mast cells [52]. PAR-2 agonists induced histamine release from human primary skin mast cells, indicating that PAR-2 may be a regulator of skin mast cell function during

cutaneous inflammation and hypersensitivity [52]. Taken together, these findings imply an important role of PAR-2 in regulating inflammatory and itch responses by a histamine-dependent mechanism, concomitant with a neurogenic mechanism via interactions between nerve fibers and mast cells [53].

Transient receptor potential channels

Transient receptor potential (TRP) channels, which are temperature sensitive, play an important role in skin biology. These channels are broadly expressed in nerve fibers and non-neuronal cells in human and animal skins, and are involved in the control of keratinocyte differentiation, inflammatory skin responses and hair growth [54].

The role of TRP channels in the modulation of itch sensations has been recently revealed. TRP vanilloid channel 1 (TRPV1) is a ligand-gated nonselective cation channel that may be activated by a wide variety of exogenous and endogenous physical and chemical stimuli, including temperature greater than 43°C, low pH (acidic conditions), the endocannabinoid anandamide, *N*-arachidonoyldopamine and capsaicin [55]. Its activation is related to action potential generation and neuropeptide release [56], but prolonged calcium influx can also desensitize primary afferent fibers [57]. TRPV1$^+$ fibers also express PAR-2 and its channel functionally interacts with PAR-2 [58]. Some effects of the PAR-2 stimulus are mediated by activation of TRPV1, indicating that TRPV1 acts synergistically with PAR-2 [59]. TRPV1 may also activate the release of proinflammatory cytokines, such as IL-1 and IL-8, in human keratinocytes [60]. TRPV1 expression is dramatically increased in lesional epidermal keratinocytes of patients with prurigo nodularis [61], and topical capsaicin is effective in this intensely pruritic disease characterized by vicious cycles of neurogenic inflammation and neurotrophin-induced nerve sprouting [62,63].

Other members of the TRP family that are activated in warm (TRPV2, TRPV3 and TRPV4) or cold (TRPM8 and TRPA1) temperature ranges may be involved in the modulation of itch sensation. Functional TRPV2, TRPV3 and TRPV4 channels are highly expressed in epidermal keratinocytes and mast cells [64–67]. Physical and thermal activation of TRPV2 causes mast cells to degranulate, a process dependent on protein kinase A-related signaling [66]. More recently, a TRPV3 mutation in mice was found to cause dermatitis and pruritus [68]. In addition, TRPV4 is activated by such lipid peroxidation products as eicosanoids, which function as TRPV1-activating pruritogenic substances [69].

Lowering skin temperature has been shown to reduce the intensity of experimentally induced itch [70]. TRPM8 is activated by menthol and icilin and may act as a therapeutic tool in the cold-mediated suppression of itch. TRPA1 also responds to cold temperature starting at about 17°C, the threshold of noxious cold for humans [71]. Moreover, the ability of TRPA1 to mediate acute and inflammatory pain is due, at least in part, to cross-talk with the signaling pathway induced by the proinflammatory peptide, bradykinin [72]. Although TRPA1 is reportedly expressed in keratinocytes, melanocytes and fibroblasts of human skin [73], the functions of TRPA1 in non-neuronal cells remain as yet unknown. Taken together, these findings indicate that TRP channels (i.e., hot and cold receptors) are involved in the modulation of not only pain, but also itch, suggesting they may be targets in the treatment of pruritus.

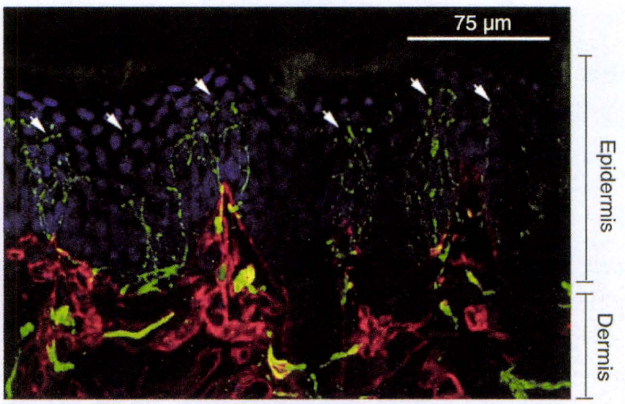

Figure 4. Epidermal nerve density in atopic dermatitis.
Skin specimens from atopic NC/Nga mice were stained with anti-PGP9.5 (green, arrows) and antinidogen (red) antibodies. Nuclei were counterstained with DAPI (blue). Scale bar: 75 µm.
DAPI: 4′, 6′-diamidino-2-phenylindole hydrochloride; PGP9.5: Protein gene product 9.5.

Leukotriene B_4

Substance P induces an arachidonate cascade to produce prostaglandins and leukotrienes. Intradermal injection of SP elicits itch responses in humans and mice. The SP-induced itch response in mice is inhibited by a phospholipase A_2 inhibitor, but not by antihistamines [49]. Glucocorticoids also inhibit itch responses in mice [49], as well as in humans [74]. The SP-induced itch response can be suppressed by a 5-lipoxygenase inhibitor, but not by cyclooxygenase inhibitors [49]. These findings indicate the involvement of arachidonate metabolites in the SP-induced itch response.

Leukotriene B_4 (LTB_4) is a potent chemotactic compound that is synthesized from arachidonic acid by 5-lipoxygenase and leukotriene A_4 (LTA_4) hydrolase [75]. LTB_4 has been shown to act as a strong pruritogen in mice [49,76]. Intradermal injection of LTB_4 was shown to induce scratching behavior in mice, but this itch response was suppressed by an antagonist against BLT1, a LTB_4 receptor [76]. This BLT1 antagonist also inhibited scratching behavior in mice induced by SP or nociceptin [77]. Moreover, SP induced the production of LTB_4 by murine epidermal keratinocytes [49], indicating that increased levels of LTB_4 in the skin can instigate the SP-induced itch response. Overall, these findings indicate that 5-lipoxygenase, LTB_4 and BLT1 may become antipruritic targets.

Opioid system

Itch in renal failure & cholestasis

Itch is common in end-stage renal failure, occurring in 40–60% of patients [78]. Recently, the Dialysis Outcomes and Practice Pattern Study (DOPPS) reported that uremic pruritus occurs with an incidence rate of 42% in hemodialysis patients [79]. Although

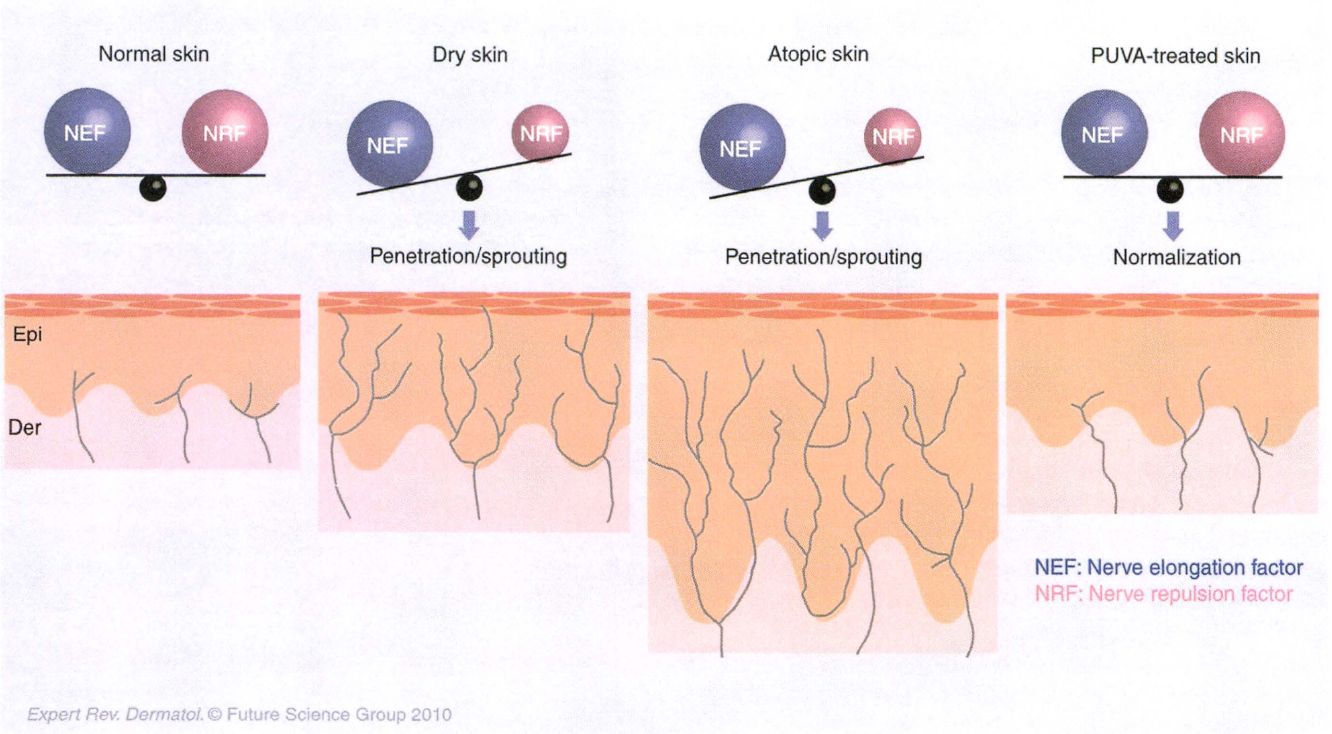

Figure 5. Regulation of epidermal nerve density by nerve elongation and repulsion factors. Epidermal NEF levels are higher, while epidermal NRF levels are lower, in dry and atopic skin than in normal skin. Abnormal NEF and NRF levels are normalized by PUVA therapy. Epidermal nerve density may be regulated by a fine balance of NEF and NRF.
Epi: Epidermis; Der: Dermis.; NEF: Nerve elongation factor; NRF: Nerve repulsion factor; PUVA: Psoralen–ultraviolet A.

secondary hyperparathyroidism, divalent ion abnormalities, histamine, allergic sensitization, proliferation of skin mast cells, iron-deficiency anemia, neuropathy and neurological changes, or a combination of these, have been hypothesized, the mechanism underlying uremic pruritus is poorly understood [80]. Currently available antipruritic drugs, including antihistamines, antiallergics and topical corticosteroids, are sometimes effective for pruritus in dialysis patients, but their efficacies are not satisfactory [78,80].

Intractable pruritus is also a frequent complication of cholestasis [78,81]. Primary biliary cirrhosis is a liver disease characterized by pruritus [81]; pruritus is estimated to occur in up to 80% of primary biliary cirrhosis patients [82]. Bile acids in the blood or skin have been considered putative pruritogens in cholestasis [83–85], but there are poor correlations between serum and subcutaneous concentrations of bile salts and intensity of itch [86,87]. The bile acid-binding resin cholestyramine was shown to be effective in a controlled trial [78], although it was associated with a high incidence of side effects. The mean plasma histamine level is significantly greater in patients with chronic cholestatic liver disease than in controls [88]. However, antihistamines are mostly ineffective against pruritus in cholestasis.

Thus, although the specific nature of the substances and the mechanisms by which they cause pruritus in chronic renal failure and cholestasis have not yet been determined, the endogenous opioid system has been demonstrated to play a role in the pathogenesis of pruritus.

μ- & κ-opioids

The μ- and κ-opioid systems play pivotal roles in the modulation of pruritus in the CNS. Opioid-induced pruritus is a well-known side effect in treating patients for pain with morphine and other μ-opioid receptor (MOR) agonists [89,90]. In contrast, MOR antagonists (e.g., naloxone and naltrexone) and κ-opioid receptor (KOR) agonists (e.g., nalfurafine) have been found to suppress pruritus in patients with chronic renal failure, cholestasis and atopic dermatitis [91]. These findings indicate that the μ-opioid system can induce itch, whereas the κ-opioid system can suppress itch at the central level (Figure 3). More recently, antipruritic effects of nalfurafine in hemodialysis patients have been validated by a Phase III, randomized double-blind placebo–controlled study [92]. Such antipruritic effects may be confirmed in cholestasis in the future studies.

Peripheral opioid systems may also play important roles in pruritus [91,93,94]. For example, topical application of MOR antagonists to the skin inhibited pruritus in patients with atopic dermatitis [95]. In addition, a peripherally restricted KOR agonist was found to antagonize chloroquine-induced scratching in mice [93]. Taken together, these findings suggest that MOR antagonists and KOR agonists have antipruritic effects at the peripheral level. Moreover, the κ-opioid system was found to be downregulated in the epidermis of patients with atopic dermatitis, whereas the μ-opioid system was at normal levels [94]. Downregulation of the μ-opioid system and restoration of the

κ-opioid system by psoralen-ultraviolet A (PUVA) therapy have been observed in patients with atopic dermatitis, concomitant with a decrease in pruritis [94]. These results suggest that epidermal opioid systems are associated with the modulation of pruritus in atopic dermatitis.

Non-neuronal opioid receptors may affect the production of cytokines, pruritogenic mediators and modulators by keratinocytes [91]. Opioids have been shown to affect the immune system, perhaps by directly targeting immune system cells [91]. Interestingly, morphine directs T cells toward Th2 differentiation [96], whereas, in mice, naloxone induces a shift from a Th2 to a Th1 cytokine pattern [97]. KOR activation decreases the inflammatory response by downregulating the production of several cytokines and chemokines, whereas MOR activation may induce a proinflammatory response [91]. To more fully assess the role of opioid systems in itch will require comprehensive assays of cytokines and pruritogens controlled by these opioid systems.

Sensory neurons also express MOR and/or KOR [98–100]. More recently, some MOR$^+$ fibers in mouse skin with atopic dermatitis have been reported to express gastrin-releasing peptide (GRP), an itch-specific mediator [101]. Thus, opioid receptors on peripheral nerve fibers may be directly linked to the modulation of itch.

Cannabinoids

Cannabinoids (CBs) have a crucial role in central and peripheral processing, and in the control of such skin-derived sensory phenomena as pain and itch [102]. The CBs bind to two G protein-coupled receptors, the cannabinoid receptors CB_1 and CB_2 [103–105]. CB_1 receptors are mainly localized in the CNS, but they are also expressed in primary afferent neurons [106–109]. CB_2 receptors are found predominantly on B and T lymphocytes, natural killer cells, monocytes and in immune organs, such as the spleen, tonsils and thymus [110], but also on rat spinal cord and human sensory nerve fibers [111]. Recently, these CB receptors have also been shown to be expressed in healthy and diseased skin [109], suggesting that alterations of the CB system may be important for the development of numerous skin diseases.

Synthetic CB agonists and/or endocannabinoids exert potent analgesic or antipruritic effects in both humans and animals by activation of CB_1 and/or CB_2 receptors, and possibly other receptors or systems (e.g., TRPV1, opioid system) at sensory nerve terminals, inflammatory cells or keratinocytes [102]. Although the mechanisms of analgesic and antipruritic effects mediated via CB receptors are controversial, the CB system is currently a possible target for future antipruritic therapy.

Abnormal itch perception resulting from an increase in epidermal nerve density

Many pruritogenic mediators and modulators released in the periphery may directly activate itch-sensitive C-fibers by binding to specific receptors on the nerve terminal. Alternatively, these molecules may act indirectly by releasing pruritogenic mediators and modulators from other cells. Nerve fibers can be activated by exogenous mechanical, chemical, and biological stimuli, resulting in itch responses.

Epidermal nerve fibers & itch

Sensory nerve fibers are acceptors of itch and pain sensations in the skin. At present, the neuronal mechanisms underlying intractable pruritus have been partly identified. Histological observations indicate that epidermal nerve fibers are present at higher densities in the skin of patients with prurigo nodularis, atopic dermatitis, psoriasis, contact dermatitis and xerosis than in control individuals. Similar findings have been observed in animal models, such as NC/Nga mice (Figure 4). These findings are indicative of increases in sensory receptors responsive to exogenous trigger factors and to various endogenous pruritogens from immune cells and keratinocytes, suggesting that hyperinnervation is partly responsible for intense itch sensations [3].

One study showed that itch is associated with low densities of nerve fibers in the epidermis and dermoepidermal junctions in lichen amyloidosis [112]. Recently, a missense mutation in the

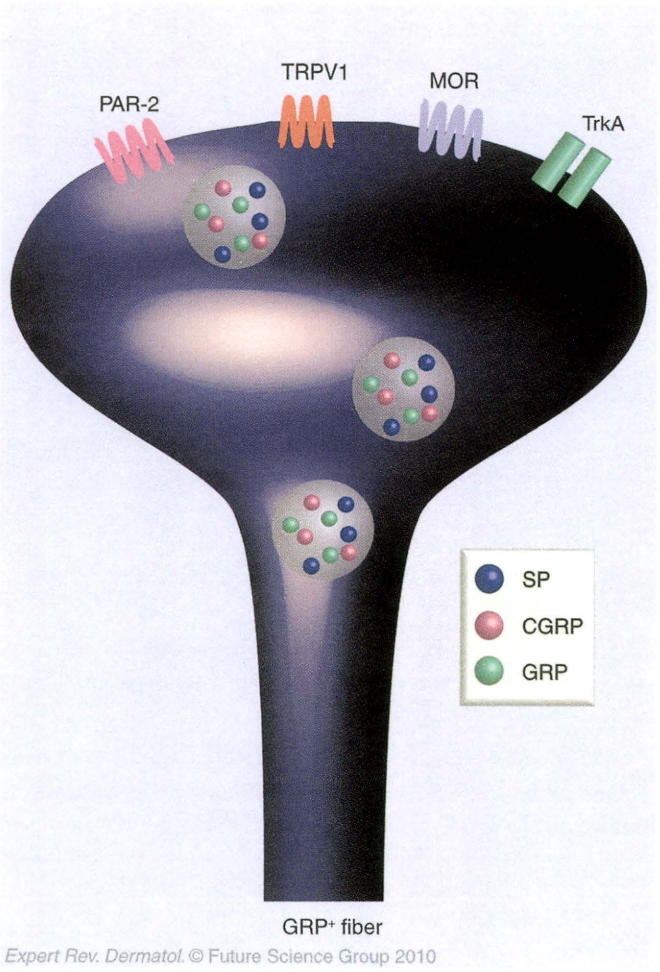

Figure 6. Properties of GRP$^+$ fibers in mouse skin. GRP$^+$ fibers contain neuropeptides such as SP and CGRP. These fibers express PAR-2, TRPV1 or MOR and are responsive to NGF.
CGRP: Calcitonin-gene-related peptide; GRP: Gastrin-releasing peptide; MOR: μ-opioid receptor; NGF: Nerve growth factor; PAR-2: Protease-activated receptor 2; TrkA: Tropomyosin-receptor-kinase A; TRPV1: Transient receptor potential vanilloid 1; SP: Substance P.

OSMR gene, which encodes oncostatin M-specific receptor β (OSMRβ), was found in three families affected by familial primary localized cutaneous amyloidosis, an autosomal dominant disorder [113]. As described above, OSMRβ is a component of the IL-31 receptor, and IL-31 is an inducer of itch [13]. In addition, IL-31 receptor and OSMRβ are expressed in afferent fibers in the spinal cord and the dermis of the skin [114]. Therefore, a cross-talk between cutaneous nerve fibers and IL-31 may induce the itch in lichen amyloidosis. Further studies are required to determine the correlation between IL-31 receptor function and nerve degeneration in lichen amyloidosis.

Moreover, such diminished skin innervation is found in the skin of patients with neuropathic itch [115]. This spontaneous itching may emanate from a CNS disorder, such as stroke, and continue in partly denervated skin. However, the mechanisms have not yet been elucidated.

Nerve elongation factors

Nerve growth factor (NGF) is a neurotrophin that affects neurite outgrowth and neuronal survival [116]. Keratinocyte-derived NGF is a major mediator of skin innervation density [116], in that the lesional skin of patients with prurigo nodularis, atopic dermatitis, psoriasis, contact dermatitis and xerosis has higher local NGF concentrations than are found in normal skin [3]. In adult rat primary sensory neurons, NGF has been shown to upregulate neuropeptides, especially SP and calcitonin-gene-related peptide (CGRP) [117], both of which are involved in the hypersensitivity of itch sensation and neurogenic inflammation [118]. Studies using NC/Nga mice have demonstrated that anti-NGF approaches significantly inhibited both epidermal nerve growth and scratching behavior, but did not ameliorate scratching that had already developed [119,120]. In addition, these anti-NGF approaches did not completely inhibit itch responses, indicating that other mechanisms may also regulate epidermal innervation.

Amphiregulin (AR), a protein belonging to the epidermal growth factor family, has been found to affect nerve fiber elongation [121,122]. AR expression was recently shown to be upregulated in the epidermis of NC/Nga mice with atopic dermatitis [123], suggesting that AR is one of the molecules regulating epidermal nerve density in the skin.

Amphiregulin has also been reported to be released from transmembrane precursors by metalloproteinases (MMPs), and this release was blocked by GM6001, a broad-spectrum MMP inhibitor, and by MMP-2/MMP-9 (i.e., gelatinase A/B) inhibitors [124]. Gelatinase activities were higher in the suprabasal layer of atopic NC/Nga mice than in controls [123]. In addition, transmembrane-type AR was found to localize on the cell surface of basal cells, but AR was diffused in the suprabasal layer. Thus, gelatinase in suprabasal cells may be involved in AR elaboration into the intercellular space between keratinocytes.

Metalloproteinase-9 has been reported to promote NGF-induced neurite elongation in PC12 cells, a neuronal cell line [125], suggesting that increased levels of gelatinase activity play a role in promoting epidermal nerve growth. In addition, pruritogens and cytokines were recently shown to upregulate keratinocyte MMP-9 production [126,127], suggesting that non-neuronal cell-derived gelatinases may contribute to the penetration of nerve fibers into the epidermis.

TNF-α is a pivotal proinflammatory cytokine in the innate immune response and a key molecule for skin inflammation. Mast cells have been identified as an important potential source of TNF-α [118]. Plasma TNF-α concentration is increased in atopic dermatitis [128], and both TNF-α and its receptors are upregulated in dermal blood vessels from patients with psoriasis [129]. A previous study using mast cell- and TNF-deficient mice demonstrated that TNF produced by mast cells promotes the elongation of epidermal and dermal nerve fibers in a mouse model of contact dermatitis [38]. Partly because of their close anatomical association, it has been suggested that cutaneous sensory nerves and mast cells can represent a functional unit whereby stimulated nerve fibers may activate local mast cells, which in turn can control local nerve function [118]. Thus, mast cell-derived TNF is one of the nerve elongation factors in inflamed skin. TNF receptors are also expressed on peripheral nerves [130]. It is possible that TNF has direct effects on sensory nerves, but the details are still uncertain. More recently, it was reported that TNF-α enhances NGF production in human keratinocytes [131]. This may imply a close relationship between mast cells and keratinocytes in nerve fiber elongation.

Nerve repulsion factors

During neural development, nerve fibers are regulated by both attraction and repulsion factors to reach its targets (e.g., skin and muscle). Semaphorin 3A (Sema3A) is a diffusible molecule that induces growth cone collapse and axonal repulsion of several neuronal populations through its interaction with a neuropilin-1 (Nrp-1)/plexin-A receptor complex [132]. Sema3A acts by selectively repelling axons from a subset of embryonic dorsal root ganglion neurons that are small in diameter and NGF-responsive [133,134]. Sema3A has been found to induce the retraction of NGF-responsive sensory afferents in adult mammalian spinal cord [135].

Semaphorin 3A transcripts are also expressed in cultured normal human epidermal keratinocytes [136]. The proteins are mainly distributed in the suprabasal layer of normal human skin [136]. Recently, epidermal Sema3A levels were reported to be lower in patients with atopic dermatitis than in healthy volunteers, concomitant with an increase in epidermal nerve density [136], indicating a good correlation between epidermal innervation and Sema3A levels. Moreover, Sema3A has been found to inhibit NGF-induced sprouting of sensory afferents in adult rat spinal cord [137], whereas elevated levels of NGF reduced the Sema3A-induced collapse of sensory growth cones [135]. These findings suggest that decreasing the expression of Sema3A can accelerate epidermal nerve growth in individuals with atopic dermatitis. Thus, epidermal innervation may be regulated by a fine balance between nerve elongation and repulsion factors (Figure 5). These findings may also provide new potential therapeutic targets for ameliorating pruritus associated with epidermal nerve density, including atopic dermatitis. The role of Sema3A in abnormal itch perception has been confirmed by recombinant Sema3A replacement

approaches in atopic NC/Nga mice [138]. More recently, abnormal Sema3A and NGF levels in atopic skin were shown to be normalized by PUVA therapy, decreasing epidermal nerve density and clinical severity scores associated with itch (Figure 5) [139]. Thus, phototherapy may become an effective treatment for pruritus involving epidermal nerve density.

Skin barrier disruption & epidermal nerve fibers

Seasonal changes affect the condition of normal skin and trigger various cutaneous disorders [2,140]. In common dermatoses, such as xerosis, atopic dermatitis and psoriasis, a decline in skin barrier function often parallels an increased severity of clinical symptomatology, including pruritus [140–142]. These conditions all tend to worsen during the winter season, when humidity is lower [140,141]. Other indirect evidence suggests that decreased humidity precipitates these disorders [143], whereas increased skin hydration appears to ameliorate these conditions [144,145]. Moreover, histological studies have shown that xerotic patients [141,146] and patients with atopic dermatitis [3] have a higher density of nerve fibers and higher levels of expression of NGF than normal individuals. Individuals with atopic dermatitis have also been found to have a significant increase in basal transepidermal water loss (TEWL), with higher TEWL also noted in clinically uninvolved skin [141].

Skin barrier disruption causes changes in epidermal innervation, making the skin more susceptible to any stimulation and sensitive to itching. This has been demonstrated in studies using acetone and acetone–ether–water (AEW)-treated mice, which are acute and chronic dry skin models, respectively [146–148]. In acetone-treated mice, the number of epidermal nerve fibers is increased [146], suggesting that nerve fibers located in the epidermal–dermal border penetrate into the epidermis by barrier disruption. Moreover, epidermal NGF and AR mRNA levels were upregulated immediately after acetone treatment, subsequently resulting in increased protein expression [146,147]. At the same time, the levels of Sema3A were decreased in the epidermis [149]. All of these changes in expression were observed before the penetration of nerve fibers into the epidermis. In one study, artificial restoration of this barrier by latex occlusion, immediately following acetone-induced barrier disruption, inhibited the increases in epidermal NGF and AR mRNAs [147,150]. Thus, alterations in cutaneous barrier permeability induced the abnormal expression of nerve elongation and repulsion factors (Figure 5), suggesting that topically applied emollient may work by normalizing the expression of the genes.

A close relationship between skin barrier disruption and itch sensation has been demonstrated by using AEW-treated mice [148]. AEW treatment elicited spontaneous scratching, concomitant with an increase in TEWL and a reduction in stratum corneum (SC) hydration. Interestingly, the treatment also induced similar spontaneous scratching in mast cell-deficient mice, indicating that mast cells may not be involved in the AEW-inducible scratching behavior. Although the mechanisms are unclear, scratching behaviors in mast cell-deficient mice may be caused, at least in part, by increases in epidermal nerve fibers or pruritogens from other dermal cells and keratinocytes.

Alternatively, water treatment following AE may be linked to the induction of spontaneous scratching, which could not be induced by organic solvents alone. Water can remove the natural moisturizing factor important for skin hydration, a factor that may impair SC hydration and flexibility [141]. Water may also induce transient swelling of the SC followed by a drying out of the surface layers. Physical swelling and shrinking might be transmitted as a mechanical stimulus to C-fibers in the upper epidermis, where it is perceived as itch. This hypothesis is supported by a recent report showing that mechanical stimuli are associated with the enhancement of neurogenic inflammation [151].

Abnormal expressions of cell–cell junctional molecules

Adherens junctions and tight junctions are critical for skin barrier function and have been shown to be altered in psoriasis [152–155] and atopic dermatitis [123]. Epidermally targeted AR-transgenic mouse strains develop many features of psoriasis spontaneously [156,157]. In these transgenic mice, the expression of E-cadherin, an adherens junction protein, is downregulated in the epidermis [158], as are the levels of expression of the tight junction proteins, zonula occludens-1 (ZO-1) and ZO-2. Levels of expression of E-cadherin and ZO-1 are also decreased in the epidermis of atopic NC/Nga mice, together with the increased expression of AR [123]. These findings suggest that AR downregulates epithelial junctional molecules in psoriatic and atopic skins, suggesting that AR affects the integrity of cell–cell junctions. These findings also imply the attenuation or abrogation of skin barrier function against external mechanical, chemical and biological stimuli in inflammatory skin diseases.

Desmosomes are complex intercellular junctions that link the keratin filaments of adjacent cells, providing mechanical strength to epithelial tissues such as the epidermis. Desmoglein 3 (Dsg3) is a desmosomal cadherin highly expressed in the basal layer of mammalian skin [159]. However, following differentiation the expression of Dsg3 decreases [159]. Electron microscopic analysis has shown that using a keratin 1 promoter induces increases in intercellular spaces in the basal and spinous layers of Dsg3-transgenic mice [160]. Dsg3 is also aberrantly expressed in the epidermis of atopic NC/Nga mice [123]. Taken together, these findings suggest a widening of intercellular spaces in the epidermis, raising the possibility that the increased spaces are required for the penetration and/or elongation of nerve fibers into the epidermis, as well as for inflammatory cell infiltration in the dermatitis [161]. Thus, epidermal hyperinnervation is enhanced by abnormal expression of cell–cell junctional molecules, and thereby may induce and/or enhance itch in skin diseases associated with barrier disruption.

GRP/GRPR system at the spinal level

Itch has long been considered a submodality or subquality of pain, because the two sensations share many similarities [1–4]. However, the neurological pathways causing itch have recently been described, with the identification of dedicated itch-sensitive C-fibers in the periphery [162] and histamine-specific spinal neurons projecting into the thalamus of the brain [163], together defining an itch-specific pathway. Interestingly, it was recently

reported that GRP plays a key role in mediating itch sensation, rather than pain, by interacting with gastrin-releasing peptide receptor (GRPR) at the spinal level [164]. Moreover, the induction of scratching behavior in response to pruritogenic stimuli was significantly diminished in GRPR mutant mice, but pain-related behavioral responses to noxious stimuli were normal [164]. In addition, direct spinal injection of a GRPR antagonist markedly inhibited scratching behaviors [164]. More recently, the specificity of the GRP/GRPR system in itch was confirmed using a saporin-conjugating bombesin technique [165]. Again, these findings provide support for the presence of a distinct itch-mediating pathway at the spinal level.

Gastrin-releasing peptide receptor mutant mice demonstrated itch induced by histamine-independent mechanisms, such as PAR-2 agonist and chloroquine treatment [164]. Meanwhile, saporin-conjugated bombesin-treated mice showed almost complete loss of scratching responses to both histamine-dependent and histamine-independent pruritogenic stimuli [165]. Moreover, different types of dorsal horn neurons are associated with histamine-induced and PAR-2-mediated itch [166]. Therefore, the observed differences suggest that GRPR$^+$ neurons in the spinal cord contain a repertoire of itch-specific signaling molecules that are programmed differentially to transmit pruritogenic signals with distinct underlying mechanisms.

Cutaneous nerve fibers containing GRP

It has been difficult to histologically identify itch-specific fibers in the skin, because no itch-specific markers have been available. However, using GRPR-mutant mice or saporin-conjugating bombesin, the GRP/GRPR system was involved specifically in itch perception via the spinal cord as described above [164,165].

More recently, GRP$^+$ fibers were histologically shown to be present in mouse skin, with the percentage of protein gene product 9.5$^+$ fibers that are GRP$^+$ being exceptionally high only in the epidermis of NC/Nga mice with atopic dermatitis [101]. Small- to medium-sized adult dorsal root ganglion neurons expressed GRP, and its receptor was present in the superficial dorsal horn. Intrathecal injection of GRP_{18-27} into wild-type mice induced scratching behavior, but did not affect pain sensitivity [164], suggesting that GRP$^+$ fibers in the skin are itch- but not pain-specific.

Moreover, GRP$^+$ fibers have been found to contain SP or CGRP and to express itch-related molecules such as TRPV1, PAR-2, MOR and TrkA, a receptor for NGF (Figure 6) [101]. However, additional research is required to determine whether GRP$^+$ fibers in human and animal skin express histamine receptors, or different types of itch-mediating fibers coexist in the periphery.

Conclusion

Considerable progress has been made in clarifying the complex pathophysiology of itch. The mechanisms of antihistamine-resistant itch may be explained by the potential roles of new histamine receptors, the participation of pruritogenic mediators and modulators other than histamine and/or neuronal sensitization (e.g., activation of itch-related receptors on sensory nerve fibers and increases in cutaneous nerve fibers and neurogenic inflammation). Accordingly, a deeper understanding of these circuits is required for the development of novel antipruritic strategies.

Expert commentary

The elucidation of histamine-mediating mechanisms for itch has progressed following the identification of H_3R or H_4R and its pathways. Animals and humans also have histamine-independent mechanisms, which may involve pruritogens other than histamine and cutaneous nerve fibers. In a recent breakthrough, the existence of an itch-specific pathway at the spinal level was demonstrated by the GRP/GRPR system. These findings will provide new insights into the basic and clinical science of itch and/or pain. The diversity of pathogenic pathways for itch is also caused by interactions among the nervous, immune and cutaneous systems. Moreover, certain modulators are involved in complex systems of itch (or pain) sensation.

Five-year view

The antihistamines that are currently used in the clinic have little, if any, affinity for H_4R. Thus, in the future, a combination of H_1R and H_4R antagonists may be the most effective treatment for individuals with histamine-dependent pruritus. Additional studies are warranted to clarify the contribution of the H_3R and H_4R to antihistamine-resistance itch. Importantly, although its role in itch needs to be demonstrated in primates, GRP/GRPR will become one of the central therapeutic targets in antipruritic drug development. Additionally, distinct neurotransmission and neuropathological patterns for itch and pain perceptions will be rapidly clarified by a multipronged approach using brain imaging, microneurography, animal models and histological techniques. Although it is generally accepted that itch is controlled by the opioid system, the underlying mechanisms remain elusive in humans and animals. Thus, further studies will be needed to elucidate the mechanisms of opioid-mediated itch. Experimentally, numerous therapeutic approaches against pruritus have been tested in animal models, especially in models of atopic dermatitis, and their antipruritic effects have been validated. Hereafter, antipruritic targets will be formulated in succession, and translational research that aims to develop therapeutic drugs will become active. These events may contribute to improvements in the quality of life of patients who suffer from intractable pruritus.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- The importance of histamine in pruritus has been shown by the elucidation of the function of H_3R or H_4R, which may become therapeutic targets in the treatment of pruritus.
- Histamine-independent mechanisms of itch are present in humans and animals, with amines, proteases, neuropeptides, cytokines, cannabinoids and opioids, and their cognate receptors, acting as mediators and/or modulators of itch.
- The itch response in the periphery is modulated by interactions among immune cells, keratinocytes and sensory nerve fibers.
- Opioid systems, especially μ and κ, control itch at the central level, and may also control itch at the peripheral level.
- Epidermal nerve density is partly responsible for abnormal itch perception in several skin diseases, and hyperinnervation is regulated by a fine balance between nerve elongation and repulsion factors.
- Skin barrier disruption induces the abnormal expression of axonal guidance molecules, thereby increasing epidermal nerve density.
- The gastrin-releasing peptide (GRP)/GRP receptor system is specifically involved in itch perception via the spinal cord.
- There is a close relationship between epidermal GRP^+ fiber density and pruritus in atopic dermatitis.

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