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Review Article

Recent Progress in Sensory Mechanism

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Abstract

Pain serves as a warning of impending injury, triggering appropriate protective responses. Emotional and cognitive processing in the brain is involved in the sensation of pain. As Ca^{2+} waves in keratinocytes are mediated by the release of extracellular molecules such as signaling molecules, this may also affect the activity of surrounding cells such as sensory neurons. Although no junctions have been found between keratinocytes and sensory termini, ultrastructural studies have shown that keratinocytes come into contact with dorsal root ganglion neurons through membrane-membrane apposition. There is also indirect evidence that keratinocytes communicate with sensory neurons via extracellular molecules. Sensory neurons themselves sense various external stimuli, but there may also be skin-derived regulatory mechanisms by which sensory signaling is modulated.

First, we will give a general outline of the subject: 1) Progress in identifying cortical loci that process pain messages is needed. 2) Far greater advances have been made in understanding the molecular mechanisms whereby primary sensory neurons detect pain-producing stimuli. 3) Genetic studies have facilitated the identification and functional characterization of molecules. 4) Now, the relationship between sensory and ion channels has become clear.

Key words: Nociceptive receptor—Odontoblast—TRPV1 channel—Purinergic receptor—ATP

Introduction

Recently, it has been demonstrated that vanilloid receptor-1 in human and rat is expressed in various tissues such skin (keratinocytes), taste cells and connective tissue (fibroblasts and odontoblasts). ATP released from keratinocytes, taste cells and odontoblasts activates primary sensory neurons via purinergic receptors and the primary sensory neurons send action potentials to the central nervous system. On the other hand, the purinoceptors of keratinocytes mediate activation via ATP.

Face area representation in primary somatosensory cortex in human

The face of the well-known somatosensory

homunculus originally described by Penfield and Boldray[35] has long been thought to be oriented upside up along the central sulcus of the human brain. The functional face mapping of the human somatosensory system is upside up, and that of the monkey is antidromic, that is to say, upside down.

Ramachandran *et al.*[36] reported a neural reorganization of the human somatosensory cortex following the loss of limb. They described a series of patients who complained of referred sensation in a phantom arm following mechanical stimulation of the chin. Yang *et al.*[44], using MEG, recorded stimulus-evoked somatosensory magnetic fields generated by the left and right cortices in seven healthy young male and female subjects. ECD location, which represents light pressure sensation for tactile sites along the lower jaw and chin, lay in a group that was separate from the rest of the face.

fMRI evidence for an inverted face representation along the central sulcus in the healthy human somatosensory cortex was provided by Servos *et al.*[38].

Thus, a precise noninvasive map was determined on the face component of the somatosensory homunculus in healthy human. The purpose of this study was to map the primary somatosensory cortex (SI) of the face area in the contralateral hemisphere in six subjects. Following stimulation of six sites on the face—infraorbital foramen, mental foramen, angle foramen, upper lip, lower lip and mandibular angle—SI and the secondary somatosensory cortex (SII) were recorded. The median nerve was stimulated as the standard of map. ECD sites estimated from field distribution were identified on the MRIs of each subject. The ECDs (M20) of early-component SEFs with peaks of 20–30 ms were aligned along the SI in the hemisphere contralateral to the stimulation site. Late components with peaks of 80–150 ms were recorded from the bilateral hemispheres, and their ECDs were identified in the SIIs of the bilateral hemispheres. There was distinct separation between ECD locations representing discrete sites on the face and thumb in the SI (M20) of the contralateral hemisphere. Five sites on the face area in SI (M20) in the contralateral hemisphere were compatible with the conventional arrangement of the homunculus in one subject. However, the remaining subjects showed variations in the arrangement. Face area reorganization in the SI is possibly due to the use-dependent cortical plasticity of the individual or perceptual experience by vision and proprioception[42].

Ca^{2+} waves in keratinocytes are transmitted to sensory neurons

The skin is the largest organ of the body and is exposed to multiple external stimuli. It protects water-rich internal organs from harmful environmental factors such as dryness, chemicals, noxious heat and UV irradiation. The skin is exposed to various substances such as ATP and bradykinin. Therefore, the skin has various sensors for environmental stimuli[12,20] or neurotransmitters[2,13,17]. Various environmental stimuli or neurotransmitters often cause in changes in $[Ca^{2+}]_i$ in the skin[9,16,19]. Ca^{2+} dynamics play an important role in the homeostasis of the skin epidermis, the outermost part of the skin tissue; the skin epidermis tunes the balance between proliferation and differentiation of epidermal keratinocytes[12,23]. Epidermal keratinocytes are non-excitable cells and do not produce action potentials[23]. Given that Ca^{2+} waves in keratinocytes are mediated by release of extracellular molecules, such signals may also affect the activities of surrounding cells such as sensory neurons. Although no junctions have been found between keratinocytes and sensory termini, ultrastructural studies have shown that keratinocytes come into contact with dorsal root ganglion (DRG) nerve fibers through membrane-membrane apposition[11]. ATP acts as an intercellular messenger in a variety of cells. The propagation of Ca^{2+} waves is mediated by extracellular ATP in culture normal human epidermal keratinocytes (NHEKs) co-cultured with DRG neurons. Furthermore, metabotropic $P2Y_2$ receptors

are expressed functionally in HNEKs[23,30]. Mechanical stimulation of NHEKs with a glass pipette induces propagation of Ca^{2+} waves in an extracellular ATP-dependent manner. In addition, Ca^{2+} waves in NHEKs could cause an increase in $[Ca^{2+}]_i$ in DRG neurons, suggesting a dynamic cross-talk between skin and sensory neurons mediated by extracellular ATP.

TRPs belong to a large family of non-selective cation channels that function in a variety of processes, including temperature sensation[5,29]. Vanilloid receptor 1 (TRPV1; VR-1) is activated by noxious heat (>42°C)[7]. TRPV2 (VRL-1) is also activated by heat, but with a higher threshold (>50°C), whereas TRPM8 (CMR1) is induced by cool/cold temperatures (<25°C)[7,8,27,34]. A receptor for innoxious warm temperature has been identified. Also, the persistent sensitivity of VR-1 knockout animals to noxious heat stimuli implies the presence of another heat receptor[6,11].

In astrocytes, extracellular molecules such as glutamate[10] and ATP[18], rather than gap junction via connexin-43, have been suggested to be important factors for Ca^{2+} waves[37].

Pain points can function as part of this mechanism. Pain points in the skin are spots that induce Ca^{2+} waves in keratinocytes and propagate signals to the primary afferent fibers. Pain points are enhanced by noxious nervous system, because the fiber terminals release capsaicin. The released capsaicin activates TRPV1 nociceptors, enhancing further evoked-noxious sensation. TRV3, VRPA1, VRPA5 and VRTA8 may be involved in taste sensation. It is suggested that VRV3 channels are involved in skin sensitization, and taste and olfactory sensation.

Vanilloid receptor expression in rat tongue and palate

Liu and Simon[24] demonstrated that capsaicin, acid, and heat all activated trigeminal neurons in rat, and that this activation was inhibited by VR1 antagonist capsazepine. This should be considered together with fact that the distribution pattern of VR1 nerves is similar to those of SP[31], CGRP[28], and purinoreceptors[3]. VR1-immunoreactive nerves in the taste papillae must be associated with nociceptive heat, acid, and capsaicin. The location of VR1 termini near taste pores or the surface of the lingual epithelium ideally places them in a position where they can play a part in monitoring the oral environment, or perceived pain.

It is interesting that epithelial VR1-immunoreactive nerves were found to be more prominent than nerves in the taste buds, which may explain the simultaneous detection of various tastes with capsaicin or heat. This idea is in harmony with the observation that local capsaicin desensitization of the human tongue does not impair taste sensation[43], while Karrer and Bartoshunk[21] reported that capsaicin changed the perception of taste, despite acting mainly on nociceptors in human.

Nozawa *et al.*[32] demonstrated VR1 expression in epithelial cells of the stomach. The cloned vanilloid receptor-1 (VR1) is recognized as a common molecular target for protein, noxious heat, and vanilloids. The presence of VR1 in the dorsal root and nodus ganglia has been firmly established, but it is unclear in the gut. VR1-immunopositive nerve endings were predominantly found in the mucous neck cells of the proliferation zone, and around blood vessels in the submucosa. The results of Nozawa *et al.*[32] indicated that VRs were expressed in rat stomach, suggesting that they might be involved in mucosal protection by increasing cell proliferation and blood flow.

The lingual epithelial expression of VR1 is partly in accord with the report of Liu and Simon[25], who used RT-PCR to demonstrate the presence of VR1 in taste receptor cells and epithelial cells in fungiform papillae. The application of capsaicin to the tongue or palate causes a burning sensation and salization[14].

Recently, ATP has been demonstrated to be the key neurotransmitter in the gustatory system. Genetic elimination of purinergic receptors ($P2X_2$ and $P2X_3$) eliminates taste

responses in the taste nerves, although the nerves remain responsive to touch, temperature, and menthol. Similarly, P2X-knockout mice show greatly reduced behavioral responses to sweeteners, glutamate, and bitter substances. Finally, stimulation of taste buds *in vitro* evokes release of ATP. Thus, ATP fulfils the criteria for a neurotransmitter linking taste buds to the nervous system[15].

Odontoblasts function as sensory receptor cell

Odontoblasts, well-polarized columnar cells at the periphery of dental pulp, originate from neural crest cells. These cells are involved in dentin formation (dentinogenesis) by the synthesis and secretion of collagenous and non-collagenous matrix protein, as well as by participating in the directional Ca^{2+} transport pathway to the dentin mineralizing front from the circulation. These events are evoked by physiological and pathophysiological chemoreceptors in dental pulp[33,40]. In addition to the Ca^{2+} signaling cascade induced by physiological and pathophysiological chemical responses in dental pulp, previous electrophysiological, molecular biological, and immunohistochemical studies have found that odontoblasts expressed mechanosensitive high conductance Ca^{2+}-activated K^+ channels[39], that a hypo-osmotic solution induced stretch-activated Ca^{2+} influx[39], and mechanosensitive TWIK (tandem of P domains in weak inward rectifier K^+ channels)-K^+ channel 1 (TREK-1)[1]. The expression of their specific phenotypes has suggested that the ionic channels in odontoblasts can mediate mechanosensitive responses to promote pathological dentin formation by a wide range of external tooth stimuli[1].

Odontoblasts are involved in the expression of dentin nociception by the following mechanisms: excitation by mechanical stimuli, noxious heat and H^+ via TRPV1 channels in the membrane; excitation of nociceptors activates cation channels through vanilloid (capsaicin) receptors; cations flow into odontoblasts, generating receptor potentials. The transmitters released from odontoblasts are ATP, which excite $P2X_3$ receptors of trigeminal afferent-fiber endings[26,42], and the impulses are propagated to the CNS. The action potentials propagating the trigeminal noxious fibers are sent antidromically to the nerve endings, and capsaicin is released[45]. The released capsaicin excites odontoblasts through vanilloid receptors, enhancing sensitivity to stimulation. Capsaicin receptors are blocked by capsazepine, a TRPV1 antagonist. A root canal disinfectant, eugenol is an agonist of capsaicin-sensitive afferent fibers. Evoked-lingual dorsum sensation affects taste sensation.

Expression of vanilloid receptor 1 in fibroblasts

VR1 expression has recently been detected in epidermis, isolated normal human keratinocytes, mast cells, and appendage epithelial structures[7,8]. However, the role of VR1 in cutaneous biology has not been clarified, although calcium-dependent keratinocyte differentiation or nociceptive regulation toward neurogenic inflammation seems to be closely involved.

Bodo *et al.*[4] and Stander *et al.*[41] have indicated a lack of VR1 immunochemical expression in the dermal fibroblast at the tissue level, but this finding needs to be investigated in cultured human skin fibroblasts. Kim *et al.*[22] explored VR1 expression in cultured human skin fibroblasts at the RNA and protein levels as compared with in human keratinocytes. HaCaT cells were used a positive control. In addition, the functional activation of VR1 was evaluated under treatment with agonists and antagonists to see whether a ligand-activity existed for the opening of cationic channels. The results of Kim *et al.*[22] suggest the existence of VR1 on fibroblasts; this receptor is likely to be influenced by ligand-dependent activation.

Summary

The problems described in this review involve sensation by peripheral afferent-fiber endings and cognitive processing by the central nervous system. These findings clarify the molecular mechanisms whereby primary sensory neurons detect sensory stimuli. Genetic studies have facilitated the identification and functional characterization of sensory molecules. The skin (keratinocytes), the taste cells and connective tissue (fibroblasts, odontoblasts) respond to stimuli. The responses to these cells are induced by mechanical stimulus, and warm thermal and H^+ stimuli via the TRPV1 channel. These responses are also induced by activation of vanilloid receptors, and by opening of cation channels. The release of transmitter ATP causes excitation of the primary afferent nerves and activates keratinocytes ($P2Y_2$ receptors), taste cells ($P2X_2$ and $P2X_3$ receptors), and odontoblasts ($P2X_3$). The ATP which keratinocytes release also enhances activation of purinoceptors ($P2Y_2$). Conversely, capsaicin released by axon reflex of afferent nerve excitation causes activation of receptor cells.

References

1) Allard B, Couble ML, Magloire H, Bleicher F (2000) Characterization and gene expression of high conductance calcium-activated potassium channels displaying mechanosensitivity in human odontoblasts. J Biol Chem 275: 25556–25561.
2) Arredondo J, Nguyen VT, Cheryavsky AI, Bercovic D, Orr-Urtreger A, Kummer W, Lips K, Vetter DE, Grando SA (2002) Central role of $\alpha 7$ nicotinic receptor in differentiation of the stratified squamous epithelium. J Cell Biol 159:325–336.
3) Bo X, Alivi A, Xiang Z, Oglesby I, Ford A, Burnstock G (1999) Localization of ATP-gated $P2X_2$ and $P2X_3$ receptor immunoreactive nerves in rat taste buds. Neuroreport 10:1107–1111.
4) Bodo E, Kovacs I, Telek A, Varga A, Paus R, Kovacs L, Biro T (2004) Vanilloid Receptor-1 (VR1) is widely expressed on various epithelial and mesenchymal cell types of human skin. J Invest Dermatol 123:410–413.
5) Calpham DE, Runnels LW, Strubing C (2001) The TRP ion channel family. Nat Rev Neurosci 2:387–396.
6) Caterina MJ, Leffler A, Malleberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, Kolzenburg M, Basbaum AI, Julius D (2000) Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 288:306–313.
7) Caterina MJ, Mark AS, Tominaga M, Rosen TA, Levine JD, Juilus D (1997) The capsaicin receptor: a heat-activated ion channel in pain pathway. Nature 389:816–824.
8) Caterina MJ, Rosen TA, Tominaga M, Brake AJ, Julius D (1990) A capsaicin-receptor homologue with a high threshold for noxious heat. Nature 398:436–441.
9) Cauna N (1973) The free penicillate nerve endings of the human hairy skin. J Anat 115: 277–288.
10) Charles AC, Merrill JE, Dirksen ER, Sanderson M (1991) Intracellular signaling in glial cells: calcium waves and oscillations in response to mechanical stimulation and glutamate. Nature 6:983–992.
11) Davis JB, Gray J, Gunthorpe MJ, Hatcher JP, Davey PT, Overend P, Harriies MH, Latcham J, Clapham C, Atkinson K, Hughes SA, Rance K, Grau E, Harper AJ, Pugh, PL, Roger DC, Bingham S, Randall A, Sheardown SA (2000) Vanilloid receptor inflammatory thermal hyperalgesia. Nature 405:183–185.
12) Denda M, Fuzisawa S, Inoue K, Akamatu H, Tomitaka A, Matsunaga K (2001) Immunoreactivity of VR1 on epithelial keratinocyte of human skin. Biochem Biophys Res Commun 285:1250–1252.
13) Dixon CJ, Bowler WB, Littlewood-Evans A, Dillon JP, Bible G, Sharpe GP, Gallangher JA (1999) Regulation of epithelial homeostasis through $P2P_2$ receptors. Br J Pharmacol 127: 1680–1686.
14) Duner-Engstrom M, Fredholm BB, Larsson O, Lundberg JM, Saria A (1986) Autonomic mechanisms underlying capsaicin-induced oral sensations and salivation in man. J Physiol 373: 87–96.
15) Finger TE, Danilova V, Barrows J, Bartel D, Vigers AJ, Stone L, Hellekant G, Kinnamon SC (2005) ATP signaling is crucial for communication from taste buds to gustatory nerves. Science 310:1495–1499.
16) Genever PG, Maxfield SJ, Kennovin GD, Maltman J, Bowgen CJ, Raxworthy MJ, Skerry TM (1999) Evidence for a novel glutamate-mediated signaling pathway in keratinocytes. J Invest Dermatol 112:337–342.

17) Grando SA (1997) Biological functions of keratinocyte cholinergic receptors. J Investig Dermatol Symp Proc 2:41–48.
18) Guthrie PB, Knappenberger J, Segal M, Bennette MV, Charles AC, Kater SB (1999) ATP released from astrocytes mediates glial calcium waves. J Neurosci 19:520–528.
19) Hilliges M, Wang L, Johansson O (1995) Ultrastructural evidence for nerve fibers with all vital layers of the human epidermis. J Invest Dermal 104:134–137.
20) Inoue K, Koizumi S, Fuziwara S, Denda S, Inoue K, Denda M (2002) Functional vanilloid receptors in cultured normal human epidermal keratinocytes. Biochem Biophys Res Commun 291:124–129.
21) Karrer T, Bartoshunk L (1995) Effects of capsaicin desensitization on taste in humans. Physiol Behav 57:421–429.
22) Kim S-J, Lee S-A, Yun SJ, Kim J-K, Park J-S, Jeong H-S, Lee J-H, Moon S-J, Won Y-H (2006) Expression of vanilloid receptor 1 in cultured fibroblast. Exp Dermatol 15:362–367.
23) Koizumi S, Fujishita K, Inoue K, Shigemoto-Mogami Y, Tsuda M, Inoue K (2004) Ca^{2+} waves in keratinocytes are transmitted to sensory neurons: the involvement to extracellular ATP and $P2Y_2$ receptor activation. Biochem J 380: 329–338.
24) Liu L, Simon SA (2000) Capsaicin, acid, and heat-evoked currents in rat trigeminal ganglion neurons: relationship of functional VR1 receptors. Physiol Behav 69:363–378.
25) Liu L, Simon SA (2001) Acidic stimuli activate two distinct pathways in taste receptor cells from rat fungiform papillae. Brain Res 923: 58–70.
26) Magloire H, Lesage F, Couble ML, Lanzdunski M, Bleicher F (2003) Expression and localization of TREK-K^+ channels in human odontoblast. J Dent Res 82:542–545.
27) McKemy DD, Neuhausser WM, Julius D (2002) Identification of a cold receptor reveals a general role of for TRP channels in thermosensation. Nature 416:52–58.
28) Montavon P, Lindstrand K (1991) Immunohistochemical localization of neuron-specific enolase and calcitonin gene-related peptide in rat taste papillae. Regul Pept 36:219–233.
29) Montell C, Birnbaumer L, Flockerzi V (2002) The TRP channels, a remarkably function family. Cells 108:595–598.
30) Nakamura F, Strittmatter SM (1996) $P2Y_1$ purinergic receptors in sensory neurons: contribution to touch-induced impulse generation. Proc Natl Acad Sci USA 93:10465–10470.
31) Nagy JI, Goedert M, Hunt SP, Bond A (1982) The nature of the substance P-containing nerve fibers in the papillae of the rat tongue. Neuroscience 7:3137–3151.
32) Nozawa Y, Nishihara K, Yamamoto A, Nakano M, Ajioka H, Matsuura N (2001) Distribution and characterization of vanilloid receptors in the rat stomach. Neurosci Lett 7:3137–3151.
33) Okumura R, Shima K, Muramatsu T, Nakagawa K, Shimono M, Suzuki T, Magloire H, Shibukawa Y (2005) The odontoblast as a sensory receptor cell? The expression of TRPV1 (VR-1) channels. Arch Histol Cytol 68: 251–257.
34) Peier AM, Moqrich A, Hergarden, AC, Reeve AJ, Andersson DA, Story GM, Early TJ, Dragori I, McIntype P, Bevan S, Patapoutian A (2002) A TRP channel that senses cold stimuli and menthol. Cell 108:705–715.
35) Penfields W, Boldray E (1937) Somatic motor sensory presentation in cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443.
36) Ramachandran VS, Stewart M, Roger-Ramachandran DC (1992) Perceptual correlates of massive cortical reorganization. Neuroreport 3:583–586.
37) Scemes E, Dermietzel R, Spray DC (1998) Calcium waves between astrocytes from Cx43 knockout mice. Glia 24:65–73.
38) Servos P, Engel SA, Gati J, Menon R (1999) fMRI evidence for an inverted face representation in human somatosensory cortex. Neuroreport 10:1393–1395.
39) Shibukawa Y, Suzuki T (1997) Measurements of cytosolic free Ca^{2+} concentration in odontoblast. Bull Tokyo Dent Coll 38:177-185.
40) Shibukawa Y, Suzuki T (2003) Ca^{2+} signaling mediated by IP_3-dependent Ca^{2+} releasing and store-operated Ca^{2+} channels in rat odontoblast. J Bone Miner Res 18:551–559.
41) Stander S, Moormann C, Schumacher M, Buddenkotte J, Artuc M, Shpacovitch V, Grzoska T, Lippert U, Henz BM, Luger TA, Metze D, Steinhoff M (2004) Expression of vanilloid receptor subtype 1 in cutaneous sensory fibers, mast cell, and epithelial cells of appendage structures. Exp Dermatol 13: 129–139.
42) Suzuki T, Shibukawa Y, Kumai T, Shintani M (2004) Face area representation of primary somatosensory cortex in humans identified by whole-head encephalograhy. Jpn J Physiol 54: 573–581.
43) Szallasi A (2001) Vanilloid receptor ligands: hopes and realities for the future. Drugs Aging 18:561–573.
44) Yang TT, Gallen CC, Schwartz BJ, Bloom FE (1993) Noninvasive somatosensory homunculus mapping in humans by using a large-array

biomagnetometer. Proc Natl Acad Sci USA 90:3098–3102.
45) Zimmermann M (2001) Pathobiology of neuropathic pain. Eur J Pharmacol 429:23–37.

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