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Positron Emission Tomography of the Human Brain in an Experimental Itch Model

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Key Words
Itch · Central nervous system · Cortex · Positron emission tomography

Introduction

The most important subjective symptom in allergy and allergic skin disease is itch. On one hand, the mechanisms of allergic inflammation are under intensive research, on the other hand investigations of the main symptom itch are hampered by the lack of experimental models. The old definition of itch as an 'unpleasant sensation eliciting the urge to scratch' was not replaced within the last 50 years of neurophysiological research [1]. However, this research was mainly focused on the mechanisms of pain sensation [2, 3]. The itch receptors are chemosensitive free endings of unmyelinated C fibers, which are a very small and slow-conducting population of cutaneous sensory nerves [4]. The recent finding of specific chemosensitive fibers has ended the controversy about the relationship of itch and pain [5]. Itch afferents are crossing in the spinal cord and are related to the brain via the lateral spinothalamic tract [4]. Little information is available on the following itch processing in the brain [6]. Results of our previous studies on objective covariates of itch using laser-evoked potentials [7], axon reflex correlations [8, 9], and a new multidimensional itch questionnaire [10] suggest a component of itch perception statistically independent of the primary stimulus intensity (histamine) or clinical severity of a pruritic disease (atopic eczema). In this study, we investigated the central nervous processing of itch by a noninvasive imaging technique.

Subjects, Material and Methods

We used an experimental itch model that delivers mediators – in this study histamine – right to the dermal-epidermal junction level, where the itch afferents have the highest density. The model was previously evaluated [8, 11]; it also allows the measurement of the C fiber activity indirectly by determination of the axon reflex, a collateral excitation of branches of afferent C fibers which then lead to vasodilatation in the periphery that can be measured by different methods. This skin puncture model was modified for a study on 6 healthy male right-handed volunteers in the positron emission tomography. Approvement from the local ethical committee was obtained. After informed and written consent, histamine dihydrochloride (Sigma) was administered at the subject's right lower

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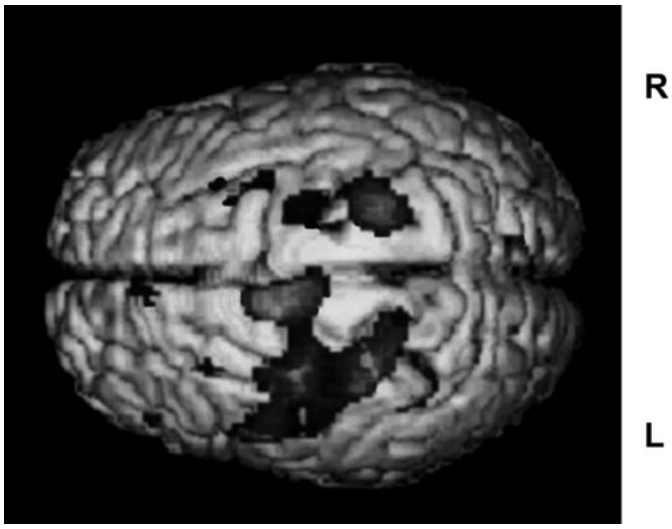

Fig. 1. Significant increase in regional blood flow after histamine stimulus at the right lower arm projected onto a 3-dimensional anatomical reference of the human brain derived from magnetic resonance imaging (voxel cluster level significance of at least $p < 0.05$). Nine repeated scans, subtraction analysis versus three saline puncture controls., n = 6.

Table 1. Significantly activated Brodmann areas after histamine itch stimulus and corresponding anatomical structures (n = 6)

Brodmann area	Anatomical structures
Left hemisphere	
6[a]	SMA
3	Gyrus postcentralis
4–6[a]	Gyrus precentralis/SMA
45–46	Gyrus frontalis medius
6–9[a]	SMA/gyrus precentralis
40	Gyrus supramarginalis
44	Gyrus precentralis
22	Gyrus temporalis superior
8	Anterior gyrus cinguli/gyrus frontalis medius
Right hemisphere	
6[a]	Gyrus precentralis/SMA
3	Gyrus postcentralis

SMA = Supplementary motor area.
[a] Correlation with subjective itch sensation (VAS) in the same Brodmann area.

arm in 9 logarithmically increasing doses from 0.03 to 8% versus NaCl control stimuli in a repeated measurement design. At a certain time point a tracer ($H_2{}^{15}O$) was injected. The scanning of the distribution of this tracer as a function of regional cerebral blood flow allows the imaging of cerebral neural activity [12–14]. After the PET scan, the itch intensity, degree of unpleasantness and the urge to scratch (not allowed) were recorded with 100-mm visual analog scales (VAS). Skin reaction diameters and VAS were correlated with neural activity. Scans were performed in darkness to reduce optically evoked cerebral activity. The scans were performed with a Siemens 951 R/31 PET scanner (CTI, Knoxville Tenn., USA) in the 3-dimensional mode. Data was transformed into the stereotactic space of Talairach and Tournoux [15]; an effective resolution of 18 mm was obtained.

Results

All 6 volunteers reported a localized pure itch sensation from 0.03% histamine on. Minimum mean intensity rating was 24%, maximum mean was 51% VAS with a very similar slope of the three subjective rating curves. Skin reactions ranged from 2 to 8 mm (wheal) and 4 to 55 mm (flare). The activation pattern versus control averaged for the 6 volunteers projected on to a nuclear magnetic resonance surface view of the brain is shown in figure 1. Several significantly activated areas could be identified. Most activations were obtained contralaterally from the stimulus. Talairach coordinates allow to project the significantly activated areas onto anatomical structures, in the end relating them to functional properties. The identified areas consist of sensory and motor regions as well as motor association areas. But also, higher integrating functional areas like gyrus frontalis medius and gyrus temporalis superior were activated. Not only the subjective itch sensation, but also the histamine concentration correlated significantly with activated areas (table 1). Correlations of skin functional parameters – temperature, flare, wheal – with these areas were also obtained. However, these associations are partially covariates of other main variables in the study like the histamine concentration.

Discussion

This first PET correlation study on itch identified functional and objective covariates of itch sensations. Itch is not represented by a single 'itch center' in the human brain. The activation patterns had some similarities with those of pain [12, 13]. The intention of pruritofensive movements like scratching – which was not allowed during the study – was mirrored by activations of motor areas in the cortex. Supplementary motor area and motor cor-

tex activation were previously described by Hsieh et al. [16] with a different stimulus paradigm at the upper arm and other PET methodology. For the first time, the sensory cortex area involvement during itch was also demonstrated in our study. Further areas are probably involved in emotional processing of the itch sensation. The possibility of determining central nervous sites involved in itch perception by correlating PET imaging and psychophysical data enables more differentiated understanding of an excruciating clinical symptom.

References

1 Shelley WB, Arthur RP: The neurohistology and neurophysiology of the itch sensation in man. Arch Dermatol 1957;76:296–323.
2 Bromm B: Laboratory animals and human volunteers in the assessment of analgesic efficacy; in Chapman RC, Loeser H (eds): Issues in Pain Measurement. New York, Raven Press, 1989, pp 117–144.
3 Bromm B, Frieling A, Lankers J: Laser-evoked brain potentials in patients with dissociated loss of pain and temperature sensibility. Electroenceph Clin Neurophysiol 1991;80:284–291.
4 Tausk F, Christian E, Johansson O, Milgram S: Neurobiology of the skin; in Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF (eds): Dermatology in General Medicine. New York, McGraw-Hill, 1993, vol 1, pp 396–403.
5 Schmidt R, Schmelz M, Forster C, Ringkamp M, Torebjörk HE, Handwerker HO: Novel classes of responsive and unresponsive C nociceptors in human skin. J Neurosci 1995;15:333–341.
6 Bernhard JD: Pruritus in skin disease; in Bernhard JD (ed): Itch. Mechanisms and Management of Pruritus. New York, McGraw-Hill, 1994, p 15.
7 Darsow U, Lorenz J, Bromm B, Ring J: Pruritus circumscriptus sine materia: A sequel of postzosteric neuralgia. Evaluation by psychophysical examination and laser-evoked potentials. Acta Derm Venereol 1996;76:45–47.
8 Darsow U, Ring J, Scharein E, Bromm B: Correlations between histamine-induced wheal, flare and itch. Arch Dermatol Res 1996;288:436–441.
9 Bromm B, Scharein E, Darsow U, Ring J: Effects of menthol and cold on histamine-induced itch and skin reactions in man. Neurosci Lett 1995;187:157–160.
10 Darsow U, Mautner V, Scharein E, Bromm B, Ring J: Der Eppendorfer Juckreizfragebogen. Hautarzt 1997;48:730–733.
11 Darsow U, Scharein E, Bromm B, Ring J: Skin testing of pruritogenic activity of histamine and cytokines at the dermal-epidermal junction level. Br J Dermatol 1997;137:415–417.
12 Jones AKP, Brown WD, Friston KJQLY, Frackowiak RSJ: Cortical and subcortical localization of response to pain in man using PET. Proc R Soc Lond B Biol Sci 1991;244:39–44.
13 Piero VD, Ferracuti S, Sabatini U, Pantano P, Cruccu G, Lenzi GL: A cerebral blood flow study on tonic pain activation in man. Pain 1994;56:167–173.
14 Raichle M: Circulatory and metabolic correlates of brain function in normal humans; in Handbook of Physiology. Bethesda, American Physiological Society, 1987, vol 5: The Nervous System, p 643–679.
15 Talairach J, Tournoux P: Co-Planar Stereotaxic Atlas of the Human Brain. Stuttgart, Thieme, 1988.
16 Hsieh JC, Hägermark Ö, Stahle-Bäckdahl M, Ericson K, Eriksson L, Stone-Elander S, Ingvar M: Urge to scratch represented in the human cerebral cortex during itch. J Neurophysiol 1994;72:3004–3008.