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Review

Central mechanisms of itch

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HIGHLIGHTS

- This review article discusses functional roles of brain regions activated by itch stimuli, in particular the primary and secondary somatosensory cortices, the cingulate cortex, and the insular cortex.
- The central mechanisms of the itch modulation system, contagious itch, and pleasurable sensation evoked by scratching are also discussed.
- The cerebral mechanism of itch partly differs between healthy subjects and chronic itch patients.

ABSTRACT

Itch is a complex sensory and emotional experience. Functional brain imaging studies have been performed to identify brain regions associated with this complex experience, and these studies reported that several brain regions are activated by itch stimuli. The possible roles of these regions in itch perception and difference in cerebral mechanism between healthy subjects and chronic itch patients are discussed in this review article. Additionally, the central itch modulation system and cerebral mechanisms of contagious itch, pleasurable sensation evoked by scratching have also been investigated in previous brain imaging studies. We also discuss how these studies advance our understanding of these mechanisms.

Contents

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1. Introduction

Itch is an unpleasant somatic sensation with the desire to scratch. To the best of our knowledge, the cerebral mechanism of itch in humans was first investigated about 20 years ago (Hsieh et al., 1994). Since then, several brain imaging studies have been conducted to understand this mechanism using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG). Most of these studies have investigated the cerebral response to physical itch-inducing stimuli such as histamine, cowhage, and electrical itch stimuli. The authors discussed the cerebral representation of itch and the possible functional roles of the identified brain regions in itch perception. Additionally, other brain imaging studies have investigated interesting phenomena related to itch. For example, itch can be suppressed by scratching or pain stimuli. Viewing itch in others and imaging the itch sensation can induce scratching responses and real itch sensations (Niemeier et al., 2000). This phenomenon is referred to as contagious itch. Moreover, scratching an itch induces a pleasurable sensation (Bin saif et al., 2012). Although the findings obtained from these studies are insufficient to fully elucidate the underlying mechanisms, several interesting findings have been reported. Thus, we also discussed these studies in this review.

2. The cerebral representation of itch

Histamine and cowhage are frequently used to induce an itch sensation. This sensation is mainly associated with the excitation of C-fibers (Schmelz et al., 1997, 2003; Namer et al., 2008). The neural signal associated with itch is further transmitted to the brain via the spinothalamic tract (STT) (Andrew and Craig, 2001). However, the itch sensation evoked by histamine and cowhage is transmitted by different populations of C-fibers and STT (Johanek et al., 2007, 2008; Davidson et al., 2007; Namer et al., 2008). Thus, to understand the mechanism of cowhage-induced itch is important for the treatment of itch that cannot be inhibited by antihistamines. Several brain imaging studies have been conducted to identify brain regions activated by itch stimuli. As shown in Fig. 1, many brain regions were found to respond to histamine- and cowhage-induced itch such as the prefrontal cortex (PFC), supplementary motor area (SMA), premotor cortex (PM), primary motor cortex (MI), primary somatosensory cortex (SI), parietal cortex, cingulate cortex, precuneus, opercular cortex (OPC) including the secondary somatosensory cortex (SII) and insular cortex (IC), claustrum, basal ganglia including the striatum, thalamus, and cerebellum (Hsieh et al., 1994; Darsow et al., 2000; Drzezga et al., 2001; Mochizuki et al., 2003, 2007, 2009; Walter et al., 2005; Leknes et al., 2007; Herde et al., 2007; Ishiuji et al., 2009; Papoiu et al., 2012). Interestingly, a previous brain imaging study reported that brain activation patterns differ between histamine- and cowhage-induced itch (Papoiu et al., 2012), suggesting that the neural mechanism of itch differs between histamine and cowhage not only in the periphery and spinal cord but also in the brain. Because the brain regions observed in the previous itch studies are also activated by pain stimuli (Treede et al., 2000; Apkarian et al., 2005), it appears that there is no brain region specifically activated by itch stimuli. Itch can also be induced by the application of electrical stimuli to the skin (Edwards et al., 1976; Shelley and Arthur, 1957; Tuckett, 1982). It has been reported that electrical stimulation most effectively generates the itch sensation for stimulus durations $\geqslant$2 ms and frequencies $\geqslant$50 Hz (Ikoma et al., 2005). Using this method, the types of peripheral nerve fibers associated with electrically induced itch were investigated using EEG (Mochizuki et al., 2008). As shown in Fig. 2A, the peak latency of the evoked potentials (EPs) to electrical itch stimuli was approximately 900 ms after the onset of these stimuli when the stimuli were applied to the wrists. By contrast, the peak latency of the EPs appeared a few hundred milliseconds earlier when the stimuli

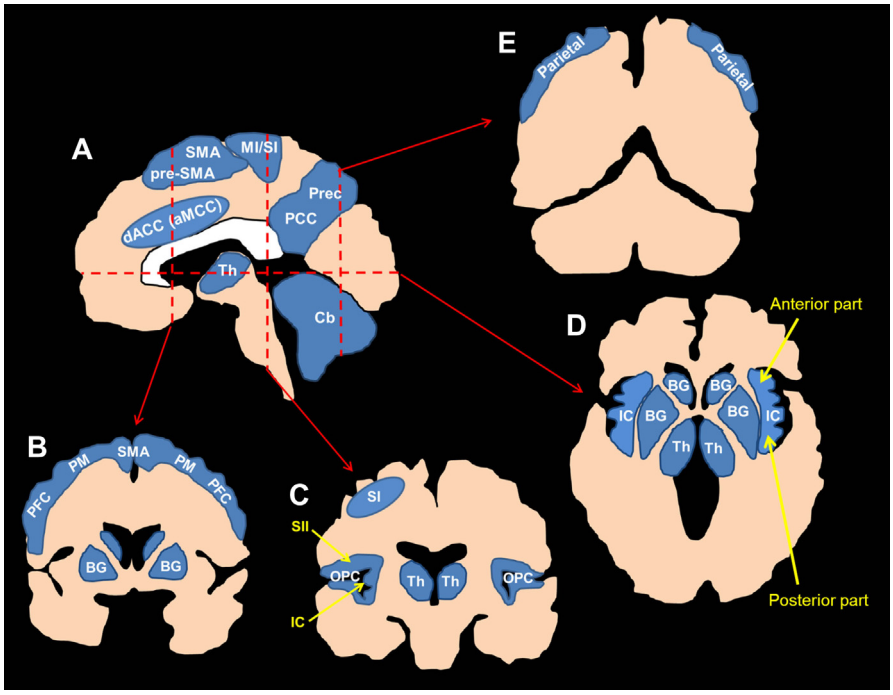

Fig. 1. Representative brain regions activated by itch stimuli. pre-SMA: pre-supplementary motor area, SMA: supplementary motor area, dACC: dorsal part of the anterior cingulate cortex, aMCC: anterior part of the midcingulate cortex, MI: primary motor cortex, SI: primary somatosensory cortex, Th: thalamus, PCC: posterior cingulate cortex, Prec: precuneus, Cb: cerebellum, PFC: prefrontal cortex, PM: premotor cortex, BG: basal ganglia, OPC: opercular cortex, SII: secondary somatosensory cortex, IC: insular cortex.