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Why does stress aggravate itch? A possible role of the amygdala.

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Abstract

Stress is the exacerbating factor of itch across patients with chronic itch due to different origins. However, the precise mechanisms behind stress-induced exacerbation of itch remain unknown. Chronic stress induces hyperexcitability of the amygdala, the center of emotional processing. Recent findings on the itch neuronal pathways support a pivotal role of the amygdala for itch processing. We hypothesized that itch is enhanced by stress through hyperexcitation of the amygdala. Modulation of amygdala activity, therefore, may have therapeutic potential in the treatment of chronic itch.

Keywords

chronic itch; amygdala; scratching; chronic stress; anxiety

Background

Stress can be categorized into two different types: acute and chronic stress. Joshua Smyth and colleagues mentioned that short duration and the return to homeostasis as two essential features of acute stressors. In contrast, they defined chronic stress as (1) repeated activations, (2) low or slow adaptation, and (3) delayed or failure to return to homeostasis [1]. Studies examining the effect of acute stress on itch have produced inconsistent findings. Viewing a standardized series of stressful images increased itch severity in patients with prurigo nodularis and lichen simplex chronicus[2]. Healthy subjects also reported higher itch from histamine iontophoresis when negative emotions were induced with violent film fragments compared to when positive emotions were induced with comedic film fragments[3]. In contrast, patients with atopic dermatitis reported lower itch scores after the Trier Social Stress Test, an established method to produce acute stress[4]. In another study, the Trier Social Stress Test did not change itch intensity and desire to scratch in patients with chronic itch[5].

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Author contribution statement

D.P. and T.A. wrote the manuscript.

Conflict of Interest

The authors have declared no competing interests.

In a rodent study, when rats were subjected to acute forced swim stress, they displayed a reduced scratching response to serotonin[6]. Divergent effects may depend on the type of stress and individual differences of its sensitivity. Certain types of acute stress may be capable of activating descending itch inhibitory pathways (e.g., the analog of stress-induced analgesia).

It is difficult to test the effects of chronic stress on itch in humans due to ethical reasons. However, significant correlations between itch and perceived stress were reported in the patients with atopic dermatitis [7,8]. In rodent studies, it has been consistently reported that chronic stress enhances itch. When subjected to four weeks of water avoidance stress, NC/Nga mice in specific pathogen-free housing developed intense scratching and dermatitis[9]. In allergic contact dermatitis model mice, chronic social isolation stress led to an increase in scratching behavior and idiopathic dermatitis, appearing in areas distinct from the contact dermatitis site[10]. Mice subjected to 10 days of water avoidance stress displayed increased scratching after injection of compound 48/80, a mast cell degranulator[11]. A 9-day heterotypic chronic intermittent stress protocol, which included cold-restraint stress, water avoidance stress, and forced swim stress, led to increased scratching (but not pain-related behavior) after serotonin injection in rats[12]. Another animal study found that a four-week chronic unpredicted mild stress (CUMS) protocol, which induced depression-like behavior in mice, led to increased scratching after injection of histamine or chloroquine, and an increase in spontaneous scratching in allergic contact dermatitis model mice[13]. Interestingly, CUMS itself led to a slight increase in spontaneous scratching without any itch induction. In spite of those findings supporting the crucial role of stress in itch, the central mechanisms underlying interactions between stress and itch remain unclear.

Premises

While many chronic itch patients report that psychological stress is a factor that aggravates their itch, the mechanisms underlying stress-induced exacerbation of itch are largely unknown. Although stressor is known to increase cortisol level, there is no correlation between itch intensity and cortisol level in the patient with atopic dermatitis [7]. There is likely cortisol-independent mechanism behind stress-induced exacerbation of itch. Stress has been reported as an aggravation factor of itch in a wide variety of pruritic conditions including dermatological or systemic diseases[14], suggesting that the final common pathway for itch processing (brain) is involved in stress-induced exacerbation of itch.

Amygdala consists of the central nucleus of the amygdala (CeA) and basolateral amygdala (BLA), including the lateral (LA) and basal (BA) nuclei, and is involved in the emotional process. Recent findings suggest a role for the amygdala in the processing of itch (Fig. 1). Itch signals are transmitted from sensory neurons to projection neurons in the spinal cord and then sent to the brain through two major pathways: the spinothalamic pathway and the spinoparabrachial pathway [15–17]. Recent genetic studies highlight the substantial role of latter pathway in itch [18,19]. Genetic silencing of CGRP-expressing neurons or genetic depletion of Vglut2 in the parabrachial nucleus decreased pruritogen-evoked scratching. Interestingly, neuronal tracing studies reveal that the parabrachial nucleus neurons send axon projections to the CeA [20,21]. It was also reported that the amygdala was activated in the

subjects received pruritic stimuli [22,23] as well as rodent models of chronic and contagious itch [24,25]. Moreover, we have recently reported that optogenetic activation of a subpopulation of amygdala neurons increased pruritogen-evoked scratching.[26]

Chronic stress (social isolation stress) induces hyperexcitability of BLA principal neurons and increases anxiety-like behaviors in rats [27]. Reduced expression of small-conductance Calcium-activated potassium channels accounts for hyperexcitability of BLA. Chronic restraint stress also induces hyperexcitability of LA and increases anxiety-like behaviors in rats that are sensitive to stress [28]. As in rodent studies, chronic stress leads to anxiety in human [29]. Human imaging studies have found amygdalar hyperactivation in subjects with high anxiety [30–33]. Anxiety level was correlated with itch in the patients with atopic dermatitis [34,35]. It is plausible to assume that chronic stress induces amygdala hyperactivation which contributes to the enhancement of itch.

Hypothesis

We hypothesized that stress aggravates itch through amygdala activation.

How to test the hypothesis

This hypothesis can be tested by investigating the role of the amygdala in increased spontaneous scratching by chronic stress in the chronic itch mouse model. Amygdala activities can be regulated using optogenetic, chemogenetic, or pharmacological manipulations. If the amygdala is involved in stress-evoked enhancement of itch, inhibition of amygdala activity should result in a decrease in enhanced spontaneous scratching.

Relevance and Perspectives

If the role of the amygdala in stress-induced exacerbation of itch is confirmed, this will open up avenues for understanding its molecular and cellular mechanisms to develop effective therapeutic strategies to treat chronic itch. Moreover, it would be worthwhile to identify the neuronal circuit of itch processing in the brain (e.g., Medial Prefrontal Cortex and Medial Cingulate Cortex)[26] and to test how chronic stress alters this circuit. Dysregulated brain circuit may be fine-tuned by pharmacological treatments, psychological interventions, or therapeutic devices.

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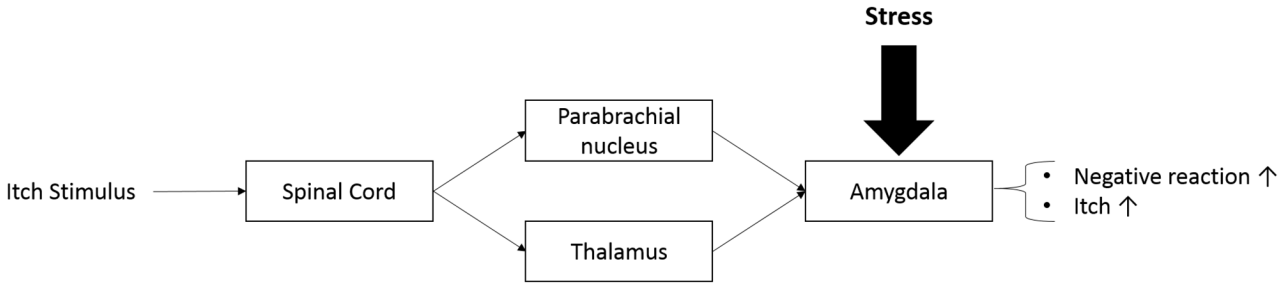

Fig. 1. Schematic diagram of a neuronal pathway that illustrates the role of the amygdala in stress-induced exacerbation of itch

The figure shows the potential pathway through which itch signals can be projected into the amygdala. Itch signals are processed through the spinothalamic pathways or spinoparabrachial pathway before being projected to the amygdala. When there is additional stress present in the environment this also acts upon the amygdala which causes an increase in negative reaction, anxiety, and itch.