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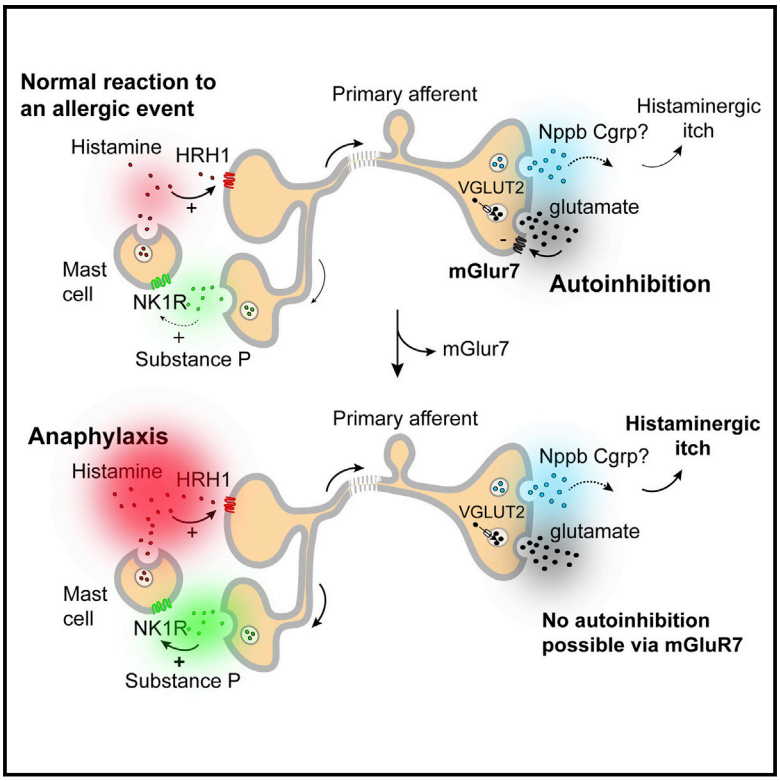
Identification of a Neuronal Receptor Controlling Anaphylaxis

Graphical Abstract



Highlights

- mGluR7 and glutamate provide autoinhibition to peripheral histaminergic neurons
- mGluR7 ablation and thus faulty regulation of peripheral neurons causes anaphylaxis
- mGluR7 regulates excessive itch via neuronal transmission in central itch pathways
- mGluR7 regulates symptoms of anaphylaxis via communication with the immune system

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In Brief

Rogoz et al. use two-photon microscopy, pharmacology, and transgenic mice to show that mGluR7 prevents local allergic events from causing anaphylaxis through presynaptic auto-regulation of peripheral neurons, indicating the role of nervous system control in anaphylaxis.

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Identification of a Neuronal Receptor Controlling Anaphylaxis

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SUMMARY

Allergic reactions can in severe cases induce a state of circulatory shock referred to as anaphylaxis. Histamine, the primary mediator of this condition, is released from immune cells, and, therefore, anaphylaxis has so far been considered an immune system disorder. However, we here show that the glutamatergic receptor mGluR7, expressed on a subpopulation of both peripheral and spinal cord neurons, controls histamine-induced communication through calcium-dependent autoinhibition with implications for anaphylaxis. Genetic ablation of mGluR7, and thus altered regulation of histamine-sensing neurons, caused an anaphylaxis-like state in *mGluR7*$^{-/-}$ mice, which could be reversed by antagonizing signaling between neurons and mast cells but not by antagonizing a central itch pathway. Our findings demonstrate the vital role of nervous system control by mGluR7 in anaphylaxis and open up possibilities for preventive strategies for this life-threatening condition.

INTRODUCTION

In 1910, intravenous β-iminazolylethylamine injections were shown to cause a sudden drop in blood pressure and respiratory disturbance (Dale and Laidlaw, 1910). The substance was later named histamine, and the accompanying clinical signs of a severe allergic reaction are now referred to as symptoms of anaphylaxis. Soon after, it was demonstrated that histamine also induces peripheral symptoms such as local itch and flare in the skin upon superficial injection (Lewis, 1927).

Histamine acts on local small diameter primary afferent neurons (Hägermark et al., 1979; Han et al., 2006; Schmelz et al., 1997), which release neurotransmitters from their central and peripheral terminals, to both relay pruritic information to the CNS and to involve the immune system in host defense. Peripheral release of neurotransmitters also leads to additional histamine discharge from nearby mast cells (Alving et al., 1991; Lawrence et al., 1987), which could potentially escalate an initially modest allergic reaction into a life-threatening systemic anaphylactic shock. Anaphylaxis is, however, an infrequent condition; the lifetime prevalence is estimated to 0.05%–2.0% (Lieberman et al., 2006). This raises the issue whether peripheral neurons are kept under control to prevent local allergic events from turning into anaphylaxis by over-stimulation of the immune system.

Histaminergic itch or pruritus is a dominating local symptom of anaphylactic shock. Pruritic events in the periphery are transmitted to the CNS by different neuropeptides, such as natriuretic polypeptide b (NPPB) (Mishra and Hoon, 2013) and calcitonin gene-related peptide (CGRP) (Rogoz et al., 2014), which are mainly confined within the transient receptor potential vanilloid 1 (TRPV1) lineage neurons (Cavanaugh et al., 2009; Mishra and Hoon, 2013). Peripheral neurons with a possible role in anaphylaxis should therefore be confined within the histamine-sensing NPPB/CGRP/TRPV1 population of primary afferents, and, if so, how is the activity of these neurons regulated?

Glutamate is a fast neurotransmitter used by most, if not all, primary afferents. Genetic ablation studies have shown that glutamate is essential for the transmission of touch and all modalities of pain (Rogoz et al., 2012; Seal et al., 2009), whereas no clear evidence has been found that glutamate released from primary afferents transmits itch. However, we and others have demonstrated that mice with impaired release of glutamate from peripheral neurons (Lagerström et al., 2010; Liu et al., 2010; Rogoz et al., 2012) displayed a profound itch behavior that could be attenuated by antihistamines (Lagerström et al., 2010). Together, these findings suggest that glutamate released from peripheral neurons rather controls and regulates histaminergic itch instead of mediating itch. If true, what could be the possible mechanism and how would that affect other components during a severe allergic reaction? We set out to investigate the neuronal component of the allergic chain to determine whether neurons, via glutamatergic signaling, might prevent a local allergic reaction from escalating into anaphylaxis.

RESULTS

Glutamate released from primary afferents binds and activates both ionotropic and metabotropic receptors. Group II/III metabotropic receptors (mGluRs) were recently shown to exert