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Review

Receptors, cells and circuits involved in pruritus of systemic disorders

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ABSTRACT

Pruritus is a sensory phenomenon accompanying a broad range of systemic disorders including hematologic and lymphoproliferative disorders, metabolic and endocrine diseases, solid tumours, and infectious diseases. The molecular mechanisms involved in itch sensation remain enigmatic in most of these diseases. However, from studies in patients and animal models a large number of mediators and receptors responsible for scratching behaviour have been identified in recent years. New insights into the interplay between neuronal and non-neuronal cells in the initiation, modulation and sensitization of itch sensation have been acquired. This review highlights the current knowledge of the molecular mechanism involved in pruritus of systemic disorders and summarizes the signalling pathways of biogenic amines, neuropeptides, proteases, eicosanoids, cytokines, opioids, endocannabinoids, neurotrophins, phospholipids and other signalling molecules participating in pruritus.

1. Introduction

Acute pruritus serves as an alarm signal to protect the body against potentially harmful environmental threats such as parasites, noxious plants or other irritants. The scratch response helps to remove these harmful agents from the skin and diminishes itch sensation. These acute forms of pruritus are mainly mediated by histamine-responsive sensory neurons in the skin that are relatively insensitive to mechanical pain stimuli but also respond to noxious chemicals such as capsaicin [1]. Chronic pruritus can be a seriously debilitating symptom accompanying various cutaneous and systemic disorders [2], but may also be caused by drugs such as the anti-malaria drug chloroquine or the volume expander hydroxyethyl starch [3]. As antihistamines do not improve itching in most of these conditions, it is likely that itch sensation is mediated via histamine-independent pathways. Recently discovered receptors involved in itch signalling of rodents such as the Mas-related G protein-coupled receptors (Mrg) for chloroquine, BAM8-22 and β-alanine [4,5], the μ-opioid receptor 1D for morphine-induced pruritus [6], endothelin-A-receptor for endothelin-1 [7], as well as the interleukin-13 [8] and interleukin-31 receptor [9] have been shown to mediate itch sensation in a histamine-independent fashion. Some of these and other receptors are G protein-coupled to phospholipase C (PLC), among which histamine-1- and serotonin-(5-HT2)-receptors activate specifically the beta 3 isoform (PLCβ3) [10,11]. Formation of intracellular signalling molecules such as diacylglycerol (DAG) and inositol-3-phosphate causes intracellular calcium release and activation of protein kinase C (PKC) resulting in opening of transient receptor potential (TRP) receptors such as the vanilloid 1 receptor (TRPV1) or ankyrin 1 channel (TRPA1) which is required for neuronal excitation [12,13] (Figs. 1–4). These primary sensory neurons signal to the dorsal horn of the spinal cord where secondary neurons are activated by the release of glutamate and the neuropeptide natriuretic polypeptide b (Nppb) [14]. These secondary, Nppb receptor expressing, neurons are suggested to release gastrin releasing peptide (GRP) which activates the GRP receptor of a third neuron in the spinal cord [14–16]. Besides the GRP-receptor also the neuromedin B-receptor has been shown to be responsible for mediating itch signals [17,18]. Ablation of either the Nppb- or GRP-receptor expressing neurons by intrathecal application of a toxin bound to the respective signalling molecule largely abolished scratching behaviour after intradermal application of various pruritogens [14,16]. Noteworthy, nociceptive (pain) stimuli were unaltered by the ablation of these neurons, indicating that a selective itch pathway exists on spinal cord level [14,16]. However, pain and itch signalling are closely intertwined processes: activation of pain neurons inhibits itch sensation, e.g. by scratching, cooling or heating of the skin [19,20], whereas antinociception can cause itch sensation, e.g. by epidural or intrathecal application of opioids or anaesthetics [21–23]. Thus, the itch circuitry was assumed to stand under a tonic inhibitory control of mechano-sensitive neurons. This hypothesis was recently strengthened by the observation of spontaneous intense scratching behaviour in mice lacking

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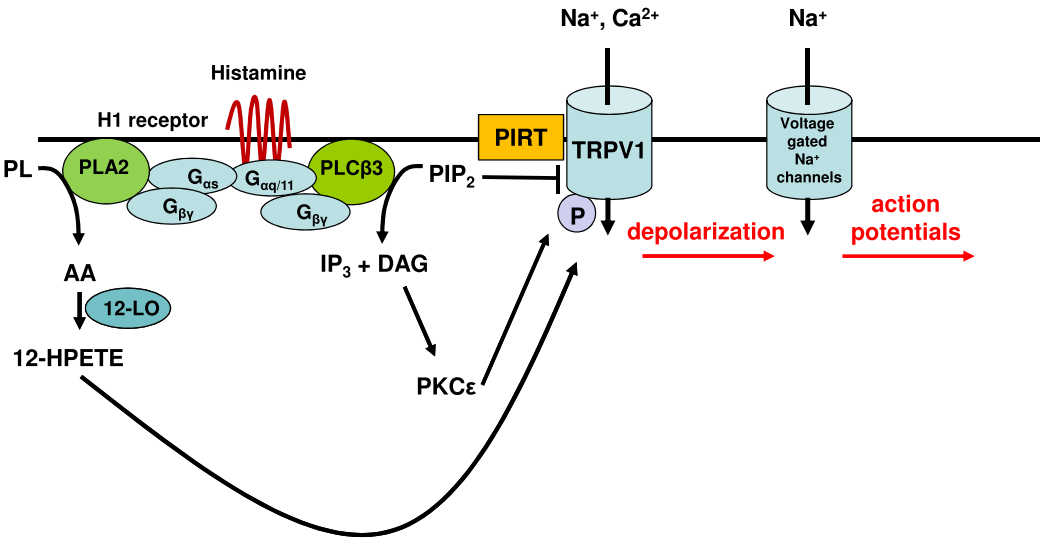

Fig. 1. Putative signalling pathway of histamine in itch neurons. For abbreviations see text.

certain inhibitory, Bhlbh5- and Prdm8-expressing interneurons [24,25]. These interneurons are believed to be activated by glutamate, as the deletion of the glutamate transporter VGLUT2 caused increased spontaneous as well as induced scratching activity after application of pruritogens (Fig. 5) [26,27]. In spite of this growing knowledge of receptors and pathways responsible for itch signalling in mice, rats and other species, the responsible ligands and receptors for itch sensation in human beings remain unidentified for most disorders associated with chronic pruritus.

Pruritus represents one of the most prominent clinical features in a wide range of systemic disorders including (*i*) hematologic and lymphoproliferative disorders such as polycythemia vera, essential thrombocytosis, primary myelofibrosis, and lymphoma, (*ii*) metabolic and endocrine diseases such as hepatobiliary diseases, chronic renal disorders, thyroid and parathyroid disorders and diabetes mellitus, (*iii*) solid tumours, (*iv*) infectious diseases, and (*v*) pruritus in the elderly.

This review summarizes the current knowledge on molecular mechanisms of pruritus associated with systemic disorders. Furthermore, the growing insight into receptors and pathways responsible for itch signalling is outlined in detail.

2. Molecular signalling pathways of pruritogens

2.1. Biogenic amines

2.1.1. Histamine

The biogenic amine histamine which is derived from the amino acid histidine, is certainly the classic itch mediator and best studied pruritogen. Intradermal application of histamine by either iontophoresis or intradermal injection causes itching after a characteristic latency of up to 1 min which is accompanied by a wheal and surrounding flare. Noteworthy, the location of application is important whether histamine acts as a pruritoceptive or nociceptive compound. Superficial cutaneous application of histamine induces pruritus whereas a deeper subcutaneous injection causes mainly pain [28]. This difference is also clinically well known: histamine release from mast cells in the dermis causes itching urticaria characterized by skin rash and wheals. In contrast, histamine liberated in subcutis, mucosa or submucosal tissue provokes angioedema being characterized by swelling of the affected tissue. This swelling is commonly painful, at least hyperalgesic and not itchy.

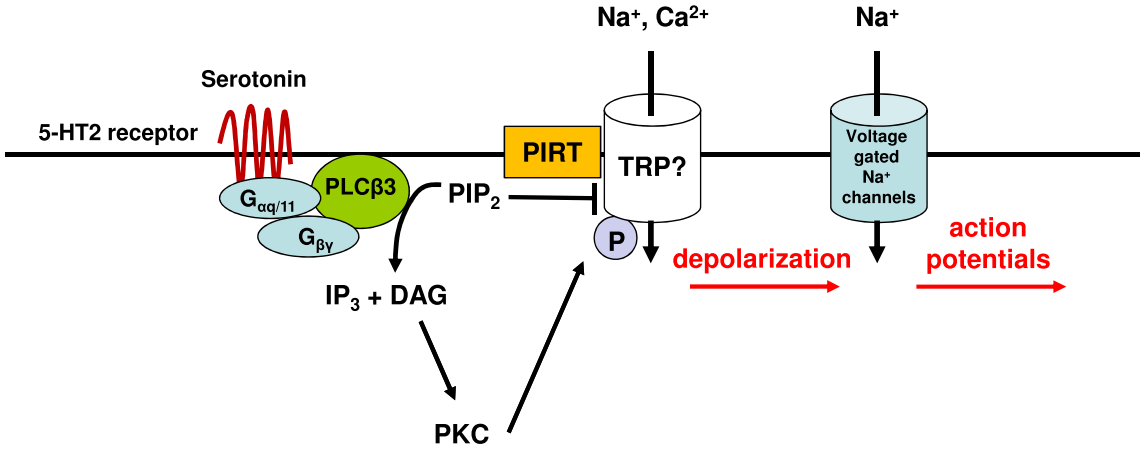

Fig. 2. Putative signalling pathway of serotonin in itch neurons. For abbreviations see text.