New antihistamines – perspectives in the treatment of some allergic and inflammatory disorders

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Introduction

Histamine [H] is a well-known biogenic amine whose biological properties were first characterized more than 100 years ago [1, 2]. It plays a significant role in the human organism as a mediator and neurotransmitter. Histamine is produced in many types of tissues including immune cells, gastric mucosa, central nervous system (CNS), smooth muscles, sensory nerves, heart, etc. Histamine-producing cells may be divided into two types: professional and non-professional [3]. Professional histamine-producing cells such as mast cells, basophils, enterochromaffin-like cells of the gastric mucosa, and histaminergic neurons synthesize this mediator, collect it in special granules inside the cells and release it in large amounts after specific stimulation. In non-professional histamine-producing cells, histamine is synthesized and crosses the cell membrane with specific carrier proteins according to the concentration gradient. The non-professional histamine-producing cells include many other cell types, among them dendritic cells (DCs) [4] and T cells [5].

Histamine is involved in numerous physiological and pathophysiological processes [6] – immunological response, immunomodulation, inflammation, allergic response, gastric acid secretion, cell proliferation, wound healing, cognitive function, memory, sleep cycle, endocrine homeostasis – and has an influence on release of other neurotransmitters [7] and modulation of tumor growth [8].

Histamine exerts its effect through four types of G-protein coupled receptors: H1, H2, H3, and H4 [6, 7, 9, 10]. Histamine interacts with its receptors with different affinities. The most susceptible are histamine H3 and H4 receptors (H3Rs and H4Rs, respectively), whereas the activation of H1 and H2 receptors (H1Rs and H2Rs, respectively) requires significantly higher concentrations of histamine [11]. It is suggested that in some disorders in which classic antihistamines (i.e. drugs antagonizing histamine effects at H1 receptors) were not effective, it might be possible to control them using novel histamine receptor ligands acting at H3 and/or H4 receptors [6, 12].

Methods of review

The authors searched the electronic database MEDLINE (PubMed, https://www.ncbi.nlm.nih.gov/pubmed/; until January 15th, 2017) using the following population search terms: H3 OR H4 combined using the Boolean operator AND with the term receptor*. These search results were focused by combination using the Boolean operator AND with the terms "Histamine Antagonists/pharmacology "[MeSH Terms] OR "Histamine Antagonists"[nm]. Results were further limited by combining (Boolean operator AND) with the aggregated (OR Boolean operator) terms related to allergic or inflammatory disorders. The following words were used as keywords: allerg*, hay fever, pollinosis, dermat*, dermatitis, dermatoses, atopic, rhinitis, rhinorrhea, conjunctiv*, rhinoconjunctivitis, prurit* itch, itching, sneezing, urticaria, congest*, asthma, cutaneous, flare, inflamm*, anaphylaxis, anaphylactic, shock, antinocicep*, nocicep*, pain*. Finally, reference lists from the resulting publications were manually searched for any relevant trials for elimination of results not related to the article topic. The resulting list of publications was limited to include only English, German, French and Spanish language publications (or at least papers with abstracts in one of the mentioned languages). Independently of the search described above, two important databases, ClinicalTrials.gov (https://clinicaltrials.gov) and EU Clinical Trials Register database (https://www.clinicaltrialsregister.eu) gathering clinical trials' results were searched using a similar strategy in order to find clinical trials not published elsewhere. In case of any doubts, also individual companies' web sites as well as the whole Internet were searched using the Google browser.

The role of histamine and its receptors in allergy and inflammation

Several immunological or non-immunological factors result in activation of histamine-producing cells and their degranulation. This biogenic amine is synthesized mainly by mast cells and basophils. The predominant storage site for histamine in most tissues is the mast cell. Therefore, the concentration of histamine is particularly high in tissues that contain large numbers of mast cells (e.g. skin, bronchial mucosa, and intestinal mucosa) [13]. An increased level of histamine within tissue rapidly activates histamine receptors (HRs) on endothelial cells and smooth muscle cells, leading to the development of such symptoms as acute rhinitis, bronchoconstriction, cramping, diarrhea, cutaneous weal and flare responses [14]. Immunological cells, as well as tissue resident cells, express a various set of histamine receptors. Two HR types, H1R and H4R, currently seem to be most important for allergic reactions and inflammatory response development. Histamine H1 receptors are very widely expressed throughout the body, amongst others in epithelial, vascular, smooth vascular, neuronal, glial, and immune cells [15–17]. H1Rs also mediate neuronal excitation; their blockade by the classical antihistamines leads to sedation [18].

The second HR important for allergic and inflammatory reactions, histamine H4 receptor, is expressed mainly on cells involved in immune/inflammatory responses. It is present at a high level on hematopoietic cells in bone marrow and peripheral immune cells such as eosinophils, mast cells, dendritic cells, and T cells [6, 19]. While H2 receptor stimulation increases cyclic AMP and causes feedback inhibition of histamine release from mast cells and basophils, activation of H_3 and H_4 receptors has the opposite effect by decreasing cellular cyclic AMP [20].

Histamine regulates a number of processes and effects crucial for the development of the inflammatory response – chemotaxis, vascular permeability, pain response – and influences the level of inflammatory mediators including its own production and release [21]. In general, the effect of histamine on a single cell depends on the cell phenotype and affinity of its receptors for histamine. For example, histamine differentially regulates T-helper-1 (Th1) and T-helper-2 (Th2) cells. Th1 cells show predominant histamine H1 receptor expression – its activation enhances IFN-γ (IFN-γ) production and Th1 proliferation [6]. Th2 cells show increased expression of histamine H2 receptor, its activation suppresses interleukin-4 (IL-4) and IL-10 production, and the suppressive effect of transforming growth factor-β (TGF-β) is potentiated as well [22]. H4R is functionally expressed on activated DC and may influence cytokine-induced differentiation of dendritic cells [6]. The DCs are professional antigen-presenting cells in the immune system of mammalians. Their primary function is to process antigen material and present it on the cell surface to the T cells [23]. Activation of H1R and H3R on DCs enhance their antigen-presenting capacity and Th1 priming whereas H2 receptor activation induces IL-10 production [6]. Histamine inhibits production of proinflammatory cytokines by monocytes IL-1, IL-12, IL-18, and tumor necrosis factor-α (TNF-α) and enhances production of IL-10. Histamine also affects antibody production by B cells [6].

Histamine is a potent mediator that plays a crucial role in the pathophysiology of several disorders and the development of many disease symptoms. This compound is one of the key mediators responsible for the development of allergic

rhinitis (AR, hay fever), pruritus, urticaria, atopic dermatitis (AD), allergic conjunctivitis and anaphylaxis [13]. It is also involved in asthma pathophysiology [6]. The essential data on the role of H and its receptors in some allergic/inflammatory diseases are summarized in Table I [24–34]. Histamine receptors' involvement will be discussed in detail in later sections.

Insufficient therapeutic potential of H1R and H2R antagonists in some allergic and inflammatory diseases

Many histamine H1 receptor antagonists are widely available over the counter and at low price. Although generally still referred to as H1R antagonists, so-called H1 antihistamines (rarely: H1R blockers) are not receptor antagonists, but are actually inverse agonists that reduce the constitutive activity of the receptor and compete with histamine [16, 35].

Currently, histamine H1 receptor antagonists continue to play a dominant role in the treatment of allergic disorders (most effective in acute types of allergy that present with symptoms of rhinitis, urticaria, and conjunctivitis; also useful as ancillary treatment in some patients with atopic dermatitis, allergic conjunctivitis, and even asthma, as well as being used unjustly in common cold) [10, 13]. These well-known applications of H1R antagonists will not be discussed in the present article.

Histamine H2 antagonists are used mainly in gastrointestinal disorders (e.g. cimetidine, ranitidine, famotidine and nizatidine). However, some H2R antagonists used as an add-on treatment to H1R antagonists may be effective in allergic disorders (see below). Nowadays, there are no new H2R antagonists intended to treat allergic and inflammatory disorders. In cases of severe or persistent urticaria refractory to treatment with H1R antihistamine alone, H2R antagonists can also be used off-label [9, 36].

Randomized controlled studies are necessary to assess whether the addition of antihistamines improves the respiratory and cardiovascular features of anaphylaxis; oral H2- (and, of course, H1-) antihistamines are thus only recommended for the relief of cutaneous symptoms of anaphylaxis, particularly the itching and urticaria [37]. It was found that the concomitant use of H1 and H2 antagonists may generate additional benefits over (and above) systemic H1-antihistamines alone in relieving some cutaneous symptoms in persons experiencing acute allergic reactions during anaphylactic reaction [38, 39]. However, the routine prophylactic use of systemic premedication with H1R and/or H2R antagonists cannot be recommended in unselected people undergoing procedures with iodinated radiocontrast media as they do not prevent life-threatening reactions [40]. There is a lack of data supporting the use of such premedication in patients with a previous reaction to another allergen [41].

Even though classical antihistamine drugs (i.e. H1R antagonists) are effective, they do not eliminate all histamine-mediated symptoms and signs; for example in allergic rhinitis the relief of some symptoms, such as congestion, is not complete [13]. Moreover, in some conditions where a histamine-dependent mechanism is responsible for the pathophysiology and symptoms only in part, such as asthma, H1R antagonists show weak activity and are used only as supplementary treatment [13]. Although there is some evidence for the role of histamine in the pathophysiology of asthma, neither H1 nor H2 antihistamines have been shown to be substantially effective for this disorder (limited efficacy, not used as sole therapy) [13]. H1R antagonists given as monotherapy proved to be ineffective in asthma [6].

Similarly, even though H1R antagonists are commonly prescribed by physicians as an adjunctive treatment along with topical corticosteroids and calcineurin inhibitors in treating pruritus in atopic dermatitis, clinical data show that these drugs have unsatisfactory effectiveness or are ineffective [42–44]. Pruritus is a histamine-dependent process, as injection of histamine into the human skin causes the sensation of itching [45]. H1 antihistamines are efficacious in reducing itching in some conditions such as acute urticaria, allergic rhinitis or insect bite reaction. However, the itch occurring in some chronic pruritic diseases, especially AD, wherein pruritus is the most disabling symptom [46], is not well controlled by these drugs (nor antihistamines targeting the H2 receptors).

Histamine H2, H3 and H4 receptors and their properties

It is now believed that histamine H3 and H4 receptors are responsible for many properties of histamine [6]. In recent years, a growing body of evidence has indicated that ligands, especially antagonists, of H4Rs (and, to a lesser extent H3Rs and even H2Rs) could play an important role in treatment of some allergic and inflammatory conditions. Therefore, distribution of these receptors and their pharmacological properties are presented below.

Distribution of H2 receptors

Strong expression of H2 receptors in the stomach and brain was demonstrated a long time ago [47]. The H2 receptor is also expressed in smooth

Table I. The role of histamine and its receptors in some allergic and inflammatory diseases

Condition/ symptom	Signs/symptoms	Histamine role in the condition	Histamine receptor(s) involvement
Allergic rhinitis	Pruritus, sneezing, rhinorrhea, nasal congestion	Major role in early symptoms of AR; degranulation of MCs with H release determines the occurrence of symptoms [6]	H1R, H3R, H4R. H1Rs are responsible for most of the AR symptoms [13]. H1RA are frequently used in AR treatment, but present minor anti-inflammatory activity [24]. Recent research indicates that additional beneficial effects of H are mediated by H3Rs and H4Rs [6]
Atopic dermatitis/ pruritus*	Itch	H indirectly induces production of IL-31, reduces the expression of Sema3A** [25–28]; H also acts directly via H1R and H4R located on sensory neurons and results in itching [27, 29]	H1R, H3R, H4R
Urticaria	Blisters, itching and angioedema as a result of vasodilatation/fluid leakage [10]; pruritus and reflex erythema following activation of sensory nerves	Release of large amounts of H from MCs; also activation of sensory nerves	Probably all the four types of HRs, but effectiveness of H2RA and H3RA is uncertain
Allergic conjunctivitis	Ocular itching, eyelid swelling, tearing, watery discharge, photophobia, and foreign body sensation with pain. Accumulation of inflammatory cells in the conjunctival mucosa occurs	Liberation of large quantities of H from conjunctival MCs after stimulation with an allergen [6]. MC-derived mediators activate vascular endothelial cells which in turn increase expression of adhesion molecules***, secretion of RANTES chemotactic chemokine, monocyte chemoattractant protein, IL-8, eotaxin and macrophage inflammatory protein-1α [30–32]	H1R, H2R, H4R
Anaphylaxis	Increased vascular permeability, smooth muscle contractions, urticaria, hypotension, dyspnea, diarrhea, abdominal cramps; taken together these processes leads to anaphylaxis [13]	Binding of antigens to IgE receptor molecules located on immunological cells leads to their activation and H and other mediators released from immunological cells causes anaphylaxis. An experimental study in the mouse systemic anaphylaxis model (HDC-KO) revealed that H is responsible for control of respiratory frequency, expiratory time and body temperature [33]	H1R, H2R (cutaneous symptoms), H4R
Asthma		Large amounts of H released by MCs stimulate other cells involved in the attack of asthma [6]. The DC are responsible for the activation of CD4+ cells. Th2 lymphocytes produce proinflammatory cytokines, e.g. IL-4, IL-5, and IL-13 during asthma attack	H4R and (to a lesser extent) H1R and H2R. H4RA decrease cytokine and chemokine production by DC and directly limit their ability to induce Th2 responses [34]. H4R is expressed on eosinophils and H is involved in their accumulation in the airways after allergic challenge [6]

*AR – allergic rhinitis, CD4+ – cluster of differentiation 4 (cells), DC – dendritic cells, H – histamine, H1RA – H1R antagonists, H1Rs – H1 receptors, H2RA – H2R antagonists, H3RA – H3R antagonists, H4RA – H4R antagonists, HDC-KO – histidine decarboxylase knockout, IgE – immunoglobulin E, IL-4 – interleukin-4, IL-5 – interleukin-5, IL-8 – interleukin-8, IL-13 – interleukin-13, IL-31 – interleukin-31, MC(s) – mast cell(s), RANTES – regulated on activation, normal T cell expressed and secreted, also known as chemokine ligand or CCL5, Sema3A – semaphorin 3A. *Pruritus is a major symptom of allergic skin diseases such as AD. **Semaphorin 3A is a guidance molecule of nerve fibers, regulator of the motility of dorsal root ganglia (DRG) growth cones as well as axonal morphogenesis [25, 26]; it inhibits extension of C-fibers in the upper layer of the epidermis and increases the level of nerve growth factor (NGF) [27, 28]. ***Intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM).*

muscle cells, chondrocytes, endothelial and epithelial cells, neutrophils, basophils, eosinophils, granulocytes (polymorphonuclear leukocytes – PMN/PML), monocytes, macrophages, DC, T cells (including γδT, T helper 1, 2), and B cells [12, 14, 22]. Activation of H2Rs also excites certain neurons [48].

Distribution of H3 receptors

H3 receptor plays important roles in multiple functions in the CNS [6]. It was shown that H3R is expressed mainly in the CNS and affects cognitive functions such as memory; disturbance of its expression may be indirectly related to the development of Alzheimer's disease [6, 49, 50]. Stimulation of H3R promotes sleep [13]. H3Rs are inhibitory autoreceptors as well as heteroreceptors with complex function. Histamine production and release in the brain is subject to feedback regulation involving H3 autoreceptors. A Large number of nonhistaminergic neurons also carry H3R; therefore a whole range of interactions between different neurotransmitter systems is possible [51].

High expression of the H3 receptor was demonstrated in the brain; it is widely distributed in very important areas of the human brain, e.g., cerebral cortex, caudate putamen, thalamus, ventromedial nucleus of the hypothalamus, and several aminergic projection systems (including histaminergic tuberomammillary nucleus – TMN neurons) and the noradrenergic neurons of the locus coeruleus [52]. In the human basal ganglia, H3 receptor was detected in the putamen, frontal cortex, globus pallidus externum, and globus pallidus internum [53]. Widespread H3R expression was also observed in rats during embryonic development in the medulla oblongata and spinal cord, as well as in brown fat [54], spinal ganglia, and in the periphery – in salivary glands, respiratory epithelium, gastric and intestinal mucosa, skin, thymus, liver, heart, and kidney [55], suggesting that H3R-mediated functions may extend beyond the CNS during development. In adult rats, the H3 receptor was found in stomach (extracellular loop (ECL) cells, also expressing histidine decarboxylase (HDC), a key enzyme in histamine synthesis) [56]. In mouse DRG, the H3 receptor is localized in medium-sized and large cells, which also expressed calcitonin gene-related peptide (CGRP). This localization may suggest that fibers containing H3R are involved in high-threshold mechanical nociception [6]. Sympathetic neurotransmitter release is regulated by H3Rs in some human and animal body structures [6], e.g. human heart [57] and dog kidney [58]. Regulation involving H3Rs also covers neuropeptide (tachykinins or CGRP) release from sensory C fibers in airways [59], skin [60], heart [57], and meninges [61].

Distribution of H4 receptors

H4R receptors occur predominantly in the peripheral immune cells, as mast cells, eosinophils, neutrophils, dendritic cells, Langerhans cells, natural killer (NK) cells, monocytes, T cells (including γδT, T helper 1, 2, Th17, and CD8 cells), keratinocytes, inflammatory dendritic epidermal cells, fibroblasts as well as (without any functional data at this stage) epithelial cells and basophils [6, 12]. Expression of H4R in nasal polyp tissue taken from patients with chronic rhinosinusitis is significantly higher than in normal nasal mucosa [62]. One recent study questions the presence of H4R in human monocytes [63]. The issue of the presence and role of H4R in brain nervous tissue has not been definitively explained [48], but there is evidence of H4R expression in non-neuronal cells in the brain [64].

Properties and features of H3 receptors and their ligands potentially relevant to anti-allergic and anti-inflammatory drug development – data from *in vitro*/animal studies

Compared to H4 receptors, there are relatively limited literature data on H3 receptors allowing anticipation of potential anti-allergic or anti-inflammatory drug development. The presence of H3 receptors was demonstrated in the epidermal layer of the human nasal mucous membrane (mainly around submucosal gland cells) [65]. Studies by Yokota *et al.* show the similar inhibition of nasal symptoms of allergic rhinitis by cetirizine and H3 receptor agonists (Sch 50971 and imetit) in mouse models [66] (chemical names of all new ligands of H3Rs and H4Rs are shown in Tables II–IV). Also, co-administration of Sch 50971 or imetit and an H1R antagonist, cetirizine, produced synergism – an inhibitory effect on nasal symptoms occurred at doses of substances that had no effect when used separately [66]. These results indicate that H3Rs are involved in the etiology of nasal allergy, and their stimulation may be useful as a novel therapeutic approach in nasal allergy. However, observations from a preclinical model of nasal congestion (NC) showed that H3Rs along with H1Rs participated in the histamine-induced NC and demonstrated the sense of simultaneously blocking both H1 and H3 receptors in conditions with NC [67, 68]. Also, compound SCH-79687 is a highly potent H3R antagonist that reduced congestion in animal models of AR when co-administered with a H1R antagonist [69]. This supports the hypothesis that the efficacy of H3R antagonists is related to peripherally mediated release of norepinephrine from nasal mucosal H3 receptors, because SCH-79687 virtually does not penetrate the brain [70].

Moreover, histamine displayed a significant role in both early-phase swelling via H1 receptors and late-phase swelling via H3/H4 receptors in a 12-O-tetradecanoylphorbol 13-acetate (TPA)-modified allergic dermatitis model in mouse earlobes established by Hirasawa and Ohuchi [71] for analyzing the role of histamine using specific HR antagonists. Earlier Hirasawa *et al.* reached a similar conclusion [72]. The effects observed suggest a possibility of effective H3R ligands' use in allergic rhinitis and possibly allergic dermatitis.

Abovementioned potential uses of H3R ligands require confirmation in clinical studies.

Table II. Names and type of action of new selective ligands of H3 receptor mentioned in the review, in alphabetical order

Ligand name	Chemical name of ligand	Type of action
JNJ39220675	(4-cyclobutyl-1,4-diazepan-1-yl)(6-(4-fluorophenoxy)pyridin-3-yl)methanone	Antagonist
PF-03654746	trans-N-ethyl-3-fluoro-3-[3-fluoro-4-(pyrrolidinylmethyl)phenyl] cyclobutanecarboxamide	Antagonist
PF-03654764	trans-3-fluoro-3-[3-fluoro-4-(pyrrolidin-1-ylmethyl)phenyl]-N-(2-methylpropyl) cyclobutanecarboxamide	Antagonist
Sch 50971	(+)-trans-4-(4(R)-methyl-3(R)-pyrolidinyl)-1H-imidazole dihydrochloride	Agonist
SCH-79687	N-(3,5-dichlorophenyl)-N'-[[4-(1H-imidazol-4-ylmethyl)phenyl]-methyl]-urea	Antagonist

Table III. Names and type of action of new dual ligands of H receptors mentioned in the review, in alphabetical order

Ligand name	Chemical name of ligand	Type of action and target receptors
GSK1004723	4-[(4-chlorophenyl)methyl]-2-({(2R)-1-[4-(4-{[3-(hexahydro-1H-azepin-1-yl)propyl] oxy}phenyl)butyl]-2-pyrrolidinyl}methyl)-1(2H)-phthalazinone	H1R/H3R antagonist
GSK835726	9H-fluoren-9-ylmethyl N-[(2S)-1-[[(2S)-6-amino-1-[(4-methyl-2-oxochromen-7-yl)amino]-1-oxohexan-2-yl]amino]-3-cyclohexyl-1-oxopropan-2-yl]carbamate; 2,2,2-trifluoroacetic acid	H1R/H3R antagonist

Table IV. Names and type of action of new selective ligands of H4 receptor mentioned in the review, in alphabetical order

Ligand name	Chemical name of ligand	Type of action
A-940894	4-piperazin-1-yl-6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-d]pyrimidin-2-ylamine	Antagonist
A-943931	4-[(3R)-3-aminopyrrolidin-1-yl]-6,7-dihydro-5H-benzo[1,2]cyclohepta[3,4-b] pyrimidin-2-amine	Antagonist
A-987306	cis-4-(piperazin-1-yl)-5,6,7a,8,9,10,11,11a-octahydrobenzofuro[2,3-h]quinazolin-2-amine	Antagonist
INCB38579	1-(7-(2-amino-6-(4-methylpiperazin-1-yl) pyrimidin-4-yl)-3, 4-dihdroisoquinolin-2(1H)-yl)-2-cyclopentylethanone	Antagonist
JNJ10191584 = VUF6002	1-[(5-chloro-1H-benzimidazol-2-yl)carbonyl]-4-methylpiperazine	Antagonist
JNJ28307474	(5-fluoro-4-methyl-2- {5-methyl-2-[4-(l-methyl-piperidin-4-yl)-butoxy]-pyridin-4yl}-lH-benzoimidazole)	Antagonist
JNJ28610244	(Z)-(5-methyl-1H-indol-2-yl)-(1-methyl-piperidin-4-yl)-methanone oxime	Agonist
JNJ38518168 (toreforant)	5-(4,6-dimethyl-1H-benzimidazol-2-yl)-4-methyl-N-[3-(1-methylpiperidin-4-yl) propyl]pyrimidin-2-amine)]	Antagonist
JNJ39758979	(R)-4-(3-amino-pyrrolidin-1-yl)-6-isopropyl-pyrimidin-2-ylamine	Antagonist
JNJ7777120	1-[(5-chloro-1H-indol-2-yl)carbonyl]-4-methylpiperazine	Antagonist
KD1157	The chemical structure of this compound has not been unveiled yet	Antagonist
UR63325	9-[3-(methylamino)azetidin-1-yl]-7-oxa-10,12-diazatricyclo[6.4.0.0(2,6)]dodeca-1(12),2(6),8,10-tetraen-11-amine	Antagonist
ZPL3893787 (PF-3893787)	4-N-(cyclopropylmethyl)-6-[(3R)-3-(methylamino)pyrrolidin-1-yl]pyrimidine-2,4-diamine]	Antagonist

Properties and features of H4 receptors and their ligands potentially relevant to anti-allergic and anti-inflammatory drug development – data from *in vitro*/animal studies

Properties and features of H4 receptors

Numerous studies have shown a regulatory effect of H4R on the influx and chemotaxis of inflammatory cells [73–76] and an inhibitory effect of H4R antagonists on these processes. H4Rs on eosinophils mediate histamine-induced eosinophil chemotaxis, a vital element of the inflammatory response in allergic rhinitis [77] and asthma [78], as well as the calcium response (increase in intracellular calcium) in eosinophils, and consistently selective H4R antagonists (JNJ7777120, A-940894 and INCB38579) hindered histamine-induced chemotaxis and calcium responses [79–82]. Chemotaxis of eosinophils evaluated indirectly by measuring the change of blood cell shape related to actin reorganization that precedes chemotaxis [83] also was blocked by H4R selective antagonists and induced by histamine and selective H4R agonists (e.g. 4-methylhistamine) [79, 80, 84–86].

In the case of mast cells, crucially important for inflammation and allergy, H4Rs seems to have an indirect modulating effect on degranulation by inducing upregulation of high-affinity IgE receptors (Fc epsilon RI – FcεRI) [87]. Similar to eosinophils, the action of histamine (and H4R agonists) at H4 receptors can produce a calcium response in mast cells as well as its chemotaxis. Histamine-induced increases in intracellular calcium can be blocked by JNJ7777120 [88]. The chemotactic effect can be blocked by H4R antagonists, but not by the antagonists of other histamine receptors [85, 88, 89]. As for data on eosinophils, changes in mast cell shape caused by chemotaxis occur and are blocked by H4R antagonists [81]. In turn, the H4R agonist 4-methylhistamine-induced chemotaxis was blocked by JNJ7777120 [84].

Moreover, the stimulation of H4R increases production of inflammatory mediators by mast cells. In mouse mast cells induction of IL-6 production and potentiation of the IL-6 production driven by LPS stimulation by histamine and the H4R agonist JNJ28610244 were blocked by H4R antagonists JNJ7777120 and JNJ28307474 [90]. In human mast cells H4R mediates the release of cytokines, leukotrienes, and chemokines [91].

Blockade of H4R also resulted in decreased proinflammatory cytokine production in intestinal [92] and airway tissues [93].

Asthma is a condition typically associated with eosinophils and mast cells [94–96]. Because of the localization and function of H_4 receptors, H4Rs may be involved in asthma pathophysiology [24, 97], for example by diminishing airway inflammation and dysfunction via modulation of Th2 cytokine function [93]. The histamine H4 receptor mediates allergic airway inflammation by regulating the activation of CD4+ T cells in mice [34]. Moreover, H4R-deficient mice and mice treated with H4R antagonists JNJ7777120 or JNJ10191584 (or VUF6002) exhibited decreased allergic lung inflammation, with decreases in infiltrating lung eosinophils/lymphocytes and Th2 responses, reduced inflammatory cytokines, as well as decreased antigen specific IgE and IgG1 levels after allergen challenge [34]. In *in vitro* studies blockade of the H4R on dendritic cells caused reduction in cytokine and chemokine production and limited their ability to induce Th2 responses in T cells [34]. Administration of H4R antagonists (JNJ7777120, JNJ39758979 or JNJ10191584) during allergen challenge also reduced the eosinophilia in animal asthma models [34, 85, 93, 98, 99]. Unexpectedly it turned out that mast cells were not needed for the H4R response in the mouse asthma models; in mice lacking mast cells inhibition of lung inflammatory cytokines levels and eosinophilia after H4R antagonists JNJ7777120 or JNJ10191584 was still present [34]. This suggests that T cells may be the main factor involved in the H4R response not in the airways only. Probably the H4 receptor plays a role in the priming and activation of T cells [45].

Reduction in Th2 cytokines has been shown in the skin after treatment with an H4R antagonist; therefore the activation of T cells may also be considered as the primary mechanism in the models of atopic dermatitis [100–103].

Several mechanisms for the H4R effect on T cells exist. Administration of H4R antagonists reduces the number of T cells at the site of inflammation in dermatitis and asthma animal models [93, 104]. The decrease in T cell number may be a result of inhibition of chemokine production [93, 100] or the immediate chemoattractive effect of histamine on T cells [105, 106]. Expression of H4R has been shown on human Th2 cells and agonists of H4R enhanced the expression of IL-31 [107]. Indirect effects on T cells also exist; H4R is involved in dendritic cell function and this way drives the response in asthma [45].

The DCs are basic antigen-presenting cells [108], important also for anaphylactic reactions. H4R in dendritic cells mediates migration of these cells to the site of interaction with T cells; migration of antigen-positive DCs from the skin to the lymph node was reduced under the influence of H4R antagonist JNJ7777120 administration [100]. Effects on DC migration may be a result of direct H4R mediation via chemoattractive action of histamine [109–113] or indirect reduction of chemo-

kine production [93, 100]. H4R modulates cytokine/chemokine production by dendritic cells that may lead to defective T cell activation [34, 109, 112–115]. H4R may also influence maturation/activation of dendritic cells [45]. The DCs can be activated by endogenous danger signals involving toll-like receptors (TLRs). The process of DC activation *in vitro* with TLR ligands, generally leading to the production of cytokines and chemokines, can be modulated by H4R antagonists [34, 109, 112–115]. It was recently established that combined blockade of the histamine H1 (loratadine) and H4 (JNJ7777120) receptor suppresses peanut-induced intestinal anaphylaxis by regulating dendritic cell function in a mouse model (effects mediated through the limitation of mesenteric lymph node and intestinal DC accumulation and function) [116].

Among inflammatory conditions, especially autoimmune disease, rheumatoid arthritis (RA) is considered as partially driven by T cell responses [45]. After administration of the H4R antagonist JNJ28307474 mice were protected from RA in two arthritis models (collagen-induced (CIAM) and collagen antibody-induced (CAIAM)), as were H4R-deficient mice [117]. Another selective H4R antagonist, JNJ39758979, also mitigated RA in the CIAM [118]. Administration of the H4R antagonist in CIAM reduced the production of IL-17 from lymphocytes and the number of Th17 cells (IL-17 positive CD4 cells) in the inguinal lymph node, but did not influence the IFN-γ production [34, 117]. Human and mouse Th17 cells displayed expression of H4R [117, 119]. Reduction of IL-17 production by H4R antagonists has been reported in models of asthma and dermatitis; also Th17 cell differentiation was blocked under the influence of these compounds *in vitro* [34, 100, 117]. The observed effects on T cells have been direct or indirect; in the CAIAM adoptive transfer of splenic CD11c+ cells (wild-type dendritic cells) restored disease in H4R-deficient animals, which indicates that the H4R on antigen presenting cells was decisive for RA activity [117]. Production of IL-17 in isolated human Th17 cells was reduced by the H4R antagonist JNJ7777120 and enhanced by an H4R agonist, suggesting a direct effect of H4R on Th17 cells [119].

Among conditions studied, an exception is experimental autoimmune encephalomyelitis – in this autoimmune condition treatment with an H4R antagonist (or lack of H4Rs) significantly worsens disease in a mouse model [75, 120].

Pruritus. A scratching response in mice induced by injection of histamine into the skin was inhibited by treatment with H4R antagonists [80, 118, 121–123], suggesting that H4R could be responsible for pruritic responses not driven by H1R. The same conclusion can be drawn with regard to the induction of scratching after injection of H4R agonists in mice, inhibition of this effect with H4R antagonists or in H4R-deficient mice [86, 122, 124–126] and to the reduction of histamine-induced scratching in H4R-deficient mice [122]. H4R antagonists inhibited scratching in animal models of dermatitis [100, 103, 123, 127, 128] and relieved scratching in mice induced by substance P [123] and haptens; in the latter case H4 receptor antagonism reduces scratching behavior but not inflammation [127].

The effects on mast cells, eosinophils, and T cells described above indicates a possibility of H4R ligands' use in such inflammatory conditions/symptoms as atopic dermatitis, asthma, allergic rhinitis, rheumatoid arthritis, pruritus or neuropathic pain in humans.

Activity of H4R ligands in animals

Preclinical evidence pointed to the key role of H4R in several histamine-related physiological and pathophysiological processes including airway inflammation, dermal inflammation, pruritus, ocular inflammation, arthritis, systemic lupus erythematosus, Sjogren's syndrome, multiple sclerosis, gastric ulcer, cancer, and pain [45, 129]. Reduction of neutrophil influx in a mouse peritonitis model was observed after pretreatment with JNJ7777120, providing the first evidence that H4R antagonists could have anti-inflammatory properties [88]. Other early research also showed that JNJ7777120 and its congener, JNJ10191584, are also effective in a rat colitis model [92]. Along with other H4R antagonists, such as JNJ10191584, JNJ39758979, JNJ28307474, A-943931 and A-987306, JNJ7777120 has demonstrated activity in models of asthma (JNJ7777120 [93, 98, 130]; JNJ7777120 and JNJ10191584 [34]; JNJ39758979 [85]), dermatitis (JNJ7777120 [101–103, 127, 128]; JNJ7777120 and JNJ28307474 [131]; JNJ28307474 [100]; JNJ39758979 [85]), pruritus (see below), arthritis (JNJ28307474 [117]) and pain (JNJ7777120 [76], A-943931 [124], A-987306 [125]). JNJ7777120 effects in models of dermatitis, asthma, arthritis, peritonitis, and pain were consistent with those obtained using other selective H4R ligands (especially antagonists) and effects in H4R-deficient animals [34, 75, 100, 117, 122]. The H4R antagonist JNJ7777120 also exerts anti-inflammatory and antifibrotic effects in bleomycin-induced lung inflammation in mice; the antifibrotic effect of JNJ7777120 is manifested by a reduction of the tissue concentration of TGF-β, collagen deposition, and smooth muscle layer thickness [132].

The importance of histamine for development of pruritus has been known for years. Recently

studies using selective H4R ligands in animal models of pruritus revealed a role for H4R in mediating chronic pruritus associated with conditions such as atopic dermatitis [27, 45, 103]. Antagonists of H4R (JNJ7777120, JNJ39758979, INCB38579 and others) reduced pruritus in a number of animal studies [80, 100, 103, 118, 122–128] as well as itching sensation in different conditions in human patients [133–136]. Blockade of H4 receptors by the compound JNJ7777120 was more efficient than H1R inhibition in a mouse model of pruritus [122]. Moreover, it was shown in two mouse models of allergen-mediated pruritus that simultaneous application of the H4R antagonist JNJ7777120 and H1R antagonist cetirizine reduced scratching bouts by up to 90% [137].

Alcaftadine, a topical ophthalmic drug indicated for the prevention of itching associated with allergic conjunctivitis, is a potent H1R and H2R antagonist (in fact, inverse agonist) with weak inverse agonistic activity also towards H4R [138, 139]; this drug acts as a functional antagonist of H4 receptor signaling [140]. Preclinical data suggest that the combination of H4R and H1R antagonists may be more effective against pruritus than an H1R antagonist alone [100, 103, 122, 127, 141]. Probably administration of H1R/H4R antagonists or co-administration of H1R and H4R antagonists will be effective also in humans.

In comparison to H1R antagonists, treatment with H4R ligands bring better results in itching, possibly caused by the additional analgesic component; a role for the H4 receptor in nociception was suggested recently. The H4R antagonist JNJ7777120 as well as its benzimidazole analog VUF6002 (JNJ10191584) had proven efficacy in a rat model of carrageenan-induced thermal hyperalgesia, increasing paw withdrawal latency [142]. JNJ7777120 was as efficacious as diclofenac (a nonsteroidal anti-inflammatory drug – NSAiD) in the same model [76]. Similar effects have also been noted with the other H4 receptor antagonists A-943931 and A-987306 in a rat carrageenan model [124, 125, 143]. Additionally, the H4 receptor antagonist A-943931 was also effective in a spinal nerve neuropathic pain ligation model [143]. An antinociceptive effect of JNJ7777120 occurred also in a subchronic inflammatory pain model induced by complete Freund's adjuvant and in a skin incision model of postoperative pain-evoking mechanical allodynia [76]. In the latter case, the maximal effect was similar to that of morphine. The same compound in a model of osteoarthritis joint pain (intra-articular injection of sodium monoiodoacetate, pain assessed by the hindlimb grip force) improved the grip force by 47% compared with a 62% improvement with celecoxib [76].

H4R antagonists have also proven to be efficacious in models of neuropathic pain. JNJ7777120 showed an effect better than that observed with gabapentin in a rat model of pain induced by chronic constriction of the sciatic or spinal nerve; its effect was maintained for 8 days, which indicates that no tolerance develops [76]. Some 2,4-diamino-5,6-disubstituted pyrimidines antagonizing histamine at H4R have also shown activity in this model [124].

The mechanisms of presented antinociceptive effects are not clear, but H4Rs in the spinal cord, dorsal root ganglion, and brain may be involved [144]. Moreover, some H4R antagonists may also act as indirect cyclooxygenase inhibitors (suppression of histamine-dependent increasing in COX-2 expression by JNJ7777120 was observed) [145].

The anti-inflammatory effect of the selective H4R antagonist JNJ7777120 was demonstrated in a mouse model of allergic rhinitis. Mice that were sensitized to ovalbumin exhibited a dose-dependent decrease in allergic rhinitis symptoms, such as sneezing and rubbing, after administration of the drug [146]. JNJ7777120 also decreased IgE concentration and increased IFN-γ level in an allergic rhinitis model in mice and rats [146, 147], including on repeated oral administration [146]. It was shown that administration of H4R antagonists A-940894 and JNJ7777120 inhibited chemotaxis and influx of immune cells, two processes also important in AR [62, 73, 81].

H4R may be an attractive pharmacological target also in the treatment of asthma [6]. Only recently studies using selective ligands in animal models of asthma showed a role for H4R in mediating lung function and inflammation [34, 45, 93, 130, 148]. The expression of H4R on immune cell types known to be involved in asthma (e.g., eosinophils, mast cells, dendritic cells, and T lymphocytes), together with the fact that H4R are involved in inflammatory processes, including cytokine production and chemotaxis, supports the idea of use of H4R antagonists in asthma. It was shown that blockade of H4 receptor leads to reduction of, characteristic for asthma, cytokine production by Th2: IL-4 (by 86%), IL-5 (95%), IL-13 (67%), IL-6 (58%) and IL-17A (by 92%) [93, 101, 146]. H4R ligands do not directly influence T cell proliferation and viability [34].

The potential clinical efficacy of H4R ligands needs to be confirmed in relevant clinical trials.

Potential drugs targeting H3 or H4 receptors in humans

In the last 20 years, an extensive search for histamine activity that did not appear to be mediated by the H1Rs and H2Rs was undertaken. From numerous conditions, for H3Rs allergic rhinitis

[149] and for H4Rs asthma and pruritus [45] appeared as areas of particular interest among immunological and inflammatory diseases. However, none of the H3R and H4R antagonists has yet to be introduced into therapy for the these disorders. There seem to be no reports yet suggesting that the possibility of H2R ligands' use as monotherapy in allergic and inflammatory disorders is real.

H3R ligands

Until recently, the only registered drug blocking H3R was betahistine, which is used in Ménière's disease, although this compound is also a weak H1 receptor agonist [150, 151], and, from March 31, 2016 pitolisant (under the name Wakix; 4.5 and 18 mg tablets, authorization valid throughout the European Union) for treating adults with narcolepsy [152]. Currently, in various stages of clinical trials there are about 20 compounds that are histamine H3 receptor antagonists (*ClinicalTrials.gov*). Another series of potent quinoline-based human H1 and H3 bivalent histamine receptor antagonists, potentially intended for intranasal administration for the treatment of AR-associated nasal congestion, was described at the end of 2016 [153]. It has been suggested that selective histamine H3 receptor antagonists may be useful in the treatment of multiple disorders, mainly CNS-related [6, 154–157]; among the many others, also use of H3R antagonists in allergic rhinitis was suggested.

Histamine H3 receptors are a novel target in the treatment of AR. Two related H3 receptor antagonists used in clinical studies were more fully characterized: PF-03654746 and PF-03654764 [158]. Single doses of PF-03654746 in combination with fexofenadine caused a reduction in allergen-induced nasal symptoms in a small trial (20 patients) providing an acute nasal allergen challenge with a bolus of ragweed [159]. In turn, combination of fexofenadine with single doses of PF-03654764 was not superior to pseudoephedrine plus fexofenadine in terms of relief of AR-associated nasal symptoms after exposure to ragweed pollen in a larger trial (n = 64). However, the PF-03654764-fexofenadine combination improved the Total Nasal Symptom Score (TNSS) compared to placebo [160]. Prophylactic treatment with the other selective H3R antagonist JNJ39220675 (10 mg, single dose) in an early clinical trial relieved allergen-induced nasal congestion by using standard nasal symptom scoring in subjects with allergic rhinitis [161]. Also a dual H1 and H3 receptor antagonist designed for intranasal administration as a suspension or solution GSK1004723 and another dual H1R/H3R antagonist, the molecule GSK835726 designed for oral administration [67, 162], as well as some 8-hydroxyquinoline derivatives [163], would be very interesting compounds, useful especially in allergic rhinitis. Two new dual antagonists of H1R/H3R, GSK1004723 and GSK835726, have undergone evaluation in clinical trials in allergic rhinitis [162]. Published results demonstrated that a single administration of 10, 50 and 100 mg GSK835726 and its repeated administration for three days at a dose of 10 mg had a similar effect as 10 mg of cetirizine [162]. The dual-acting H1R/H3R antagonist GSK1004723 given by the intranasal route has completed two phase 2 clinical trials in human volunteers with allergic rhinitis; results indicate its efficacy (*ClinicalTrials.gov*, NCT00824356 and NCT00972504). GSK1004723 reduced nasal symptoms of AR, but the effect was smaller compared to GSK835726 and cetirizine [162, 164]. GSK1004723 has been defined as a compound with long action duration and a pharmacokinetic profile suitable for once a day dosing and intranasal application [67].

H4R ligands

In clinical practice, currently there are no drugs that block the histamine H4 receptor activity selectively. The first potent and selective H4R antagonist, JNJ7777120, was described in 2003 along with another selective H4R antagonist that is a 7-NH2 substituted indolyl-piperazine derivative [165]. Currently, several dozen H4R ligands are known (most of these are antagonists); a large portion of them were synthesized and described only recently [166, 167]. Because of the H4R distribution pattern, histamine H4 receptor antagonists (first of all, JNJ7777120, toreforant [JNJ38518168], JNJ3975897 and ZPL3893787 [formerly PF-3893787]) appear to be useful especially for the treatment of inflammatory and allergic disorders [133].

Clinical reports with H4R antagonists are few, mostly concerning JNJ39758979, a potent and selective H4R antagonist that earlier demonstrated its effectiveness in animal models of dermatitis, pruritus, asthma, and arthritis [85, 118]. Results of studies evaluating H4R antagonists in animal pruritus models indicated that these compounds could also be effective in humans [100–103, 128]. Indeed, the anti-pruritic effect of H4R antagonists recently has also been demonstrated in clinical studies; the selective H4R antagonist JNJ39758979 alleviated pruritus in patients with atopic dermatitis [134] and inhibited histamine-induced pruritus in healthy volunteers [135]. In the latter study, a role of H4R in mediating histamine-induced pruritus in humans was examined. Histamine was injected intradermally into the skin of the forearm of subjects given 2 or 6 h previously a single dose of JNJ39758979 or the H1R antagonist cetirizine, or placebo, and the pruritic response was assessed. JNJ39758979 significantly relieved the

histamine-induced itch sensation at both 2 and 6 h after drug administration, cetirizine reduced the pruritic response at 6 h after treatment, whereas placebo had no effects. JNJ39758979 did not affect wheal and flare reactions, whereas cetirizine reduced both itching and wheal and flare [135] (*ClinicalTrials.gov*, NCT01068223).

However, in the case of atopic dermatitis, also evidence from clinical studies exists that the H4R antagonist JNJ39758979 can be efficacious against this condition in humans, but potentially dangerous. Two doses of JNJ39758979 (100 and 300 mg) were compared with placebo in a phase 2a study in adults with moderate AD [136]. JNJ39758979 proved to be effective at week 6 of treatment using eczema area and severity index (EASI) scores, but the study was terminated before the treatment completion as a result of two cases of agranulocytosis. This adverse effect was most likely connected with reactive metabolites of JNJ39758979, not with H4R antagonism [136]. A reduction in the EASI score was noted for both drug doses in comparison with placebo, but the differences were not statistically significant. Secondary endpoints were used to assess pruritus, the most characteristic and common symptom of AD, because the EASI score does not provide direct pruritus measurement. Analysis of these endpoints demonstrated strong and significant reduction in the pruritus after JNJ39758979 administration [136]. It can be concluded that other H4R antagonists devoid of serious adverse effects could be effective in the treatment of AD, particularly pruritus in its course. Alcaftadine, a potent H1R antagonist and weak H4R antagonist, is more effective in reducing ocular itch in comparison with olopatadine (H1R antagonist without H4R activity) after conjunctival allergen challenge in humans [168]. Taken together, these results indicate that H4R is involved in mediating pruritic responses in humans, and that H4R antagonists should be effective in the treatment of pruritic histamine-mediated conditions, such as atopic dermatitis, acute urticaria, allergic rhinitis or allergic conjunctivitis. A good example of a condition where the itching sensation is not well controlled by H1R antagonists is AD, a common inflammatory pruritic skin disease [169].

Several compounds acting on the H4 receptor are currently under evaluation in clinical trials. Janssen Pharmaceuticals was exploring the usefulness of toreforant (JNJ38518168), the first H4R antagonist with a generic name in the treatment of asthma (*ClinicalTrials.gov*, NCT01823016) and rheumatoid arthritis in patients with active disease despite methotrexate therapy (Phase II trials; *ClinicalTrials.gov*, NCT01862224 and dose range finding study NCT01679951). The asthma study (NCT01823016) was completed in July 2015, but no study results were posted on *ClinicalTrials.gov* as of January 15, 2017. Both rheumatoid arthritis studies (NCT01679951 and NCT01862224) were prematurely terminated, the second because of lack of efficacy in the first. Also an efficacy and safety study of JNJ38518168 in adult participants with RA (*ClinicalTrials.gov*, NCT00941707, sponsor: Johnson & Johnson) was prematurely terminated due to a single, unexpected serious event (details not given at *ClinicalTrials.gov*). A clinical study evaluating safety and efficacy of toreforant in patients with moderate to severe plaque-type psoriasis (*ClinicalTrials.gov*, NCT02295865) was completed, but no study results were posted on *ClinicalTrials.gov* as of January 15, 2017.

In patients with persistent asthma, also a study with the potent and selective H4R antagonist JNJ39758979 has been completed (*ClinicalTrials.gov*, NCT00946569, sponsor: Johnson & Johnson), but no data had been reported on *ClinicalTrials.gov* as of January 15, 2017.

Ziarco Pharma (UK) completed a phase II clinical trial for compound ZPL3893787, a H4 antagonist, which confirmed its safety and highly advantageous pharmacokinetic properties in subjects with atopic dermatitis (*ClinicalTrials.gov*, NCT02424253) [133]. This compound was also assessed in a bronchial allergen challenge study in patients with asthma (*ClinicalTrials.gov*, NCT00856687, completed). In both cases no study results were posted on *ClinicalTrials.gov* as of January 15, 2017.

Currently, phase II clinical trials (proof of concept) are being performed, or have been completed, for the spray KD1157 (H4 antagonist, Kalypsys Inc. company; however, the chemical structure of this compound has not been revealed [166] and the website of this firm is not active [as of January 15, 2017, at http://www.biocentury.com/companies/kalypsys_inc]) with the goal of replacing intranasal steroid therapy as the preferred treatment for the relief of congestion in allergic rhinitis [133] and tablets UR63325 (H4 antagonist, Draconis Pharma) in a nasal allergen challenge study in patients with allergic rhinitis (*ClinicalTrials.gov*, NCT01260753). This latter study was completed, but no study results were posted on *ClinicalTrials.gov* as of January 15, 2017.

Conclusions

Histamine receptor ligands are widely used in the treatment of many allergic diseases, e.g. allergic rhinoconjunctivitis, urticaria, or atopic dermatitis. H1R and H2R antagonists are among the most frequently used drugs in self-treatment by patients. Novel generations of H1R antagonists are safer and adverse effects are limited. Appropriate-

ly administered and when avoiding dangerous interactions, second-generation H1-antihistamines are relatively safe [13]. However, in many allergic and inflammatory disorders the therapeutic potential of H1RA (as well as H2RA) is relatively low. Therefore, high expectations are placed on novel ligands of histamine H3 and H4 receptors. The role of these receptors is not fully understood yet, but the last years have significantly increased our understanding of their functions. Over recent years, researchers have focused on understanding of their location and mechanism of action. Although remaining in the minority, potential peripheral (i.e., not related to the CNS) indications of H3R inhibitors have also been explored (allergic rhinitis, allergen-induced nasal symptoms, possibly also allergic dermatitis). The H4 receptor is a novel, attractive drug target for a range of conditions, in particular in disorders associated with inflammation or allergies. H4R antagonists presented high efficacy and relative safety in animal models and currently several clinical trials involving them are being conducted or were recently completed. However, there is still much to be examined. The full therapeutic potential of H3 receptor and H4 receptor ligands is far from understood. There are many remaining questions, especially with regard to the characterization of the latest discovered H4 receptor (as to the full complement of cells that express H4R, potential functions beyond inflammation, such as in the CNS or peripheral nervous system). In conclusion, therapeutic prospects are promising (particularly in relieving such a disabling condition as pruritus), but it is too early to be able to say that the treatment will revolutionize the field.

Conflict of interest

The authors declare no conflict of interest.

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