Enigmatic Histamine Receptor H4 for Potential Treatment of Multiple Inflammatory, Autoimmune, and Related Diseases

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Abstract: The histamine H4 receptor, belonging to the family of G-protein coupled receptors, is an increasingly attractive drug target. It plays an indispensable role in many cellular pathways, and numerous H4R ligands are being studied for the treatment of several inflammatory, allergic, and autoimmune disorders, including pulmonary fibrosis. Activation of H4R is involved in cytokine production and mediates mast cell activation and eosinophil chemotaxis. The importance of this receptor has also been shown in inflammatory models: peritonitis, respiratory tract inflammation, colitis, osteoarthritis, and rheumatoid arthritis. Recent studies suggest that H4R acts as a modulator in cancer, neuropathic pain, vestibular disorders, and type-2 diabetes, however, its role is still not fully understood.

Keywords: histamine H4 receptor; G protein-coupled receptors; allergic diseases; inflammatory diseases; autoimmune disorders; neuropathic pain; cancer

1. Introduction

Histamine action via distinct receptors (H1R–H4R) modulates diverse physiological as well as pathological processes. Due to their differential receptor pharmacology and signal transduction properties, histamine has characteristic effects dependent upon the histamine receptor subtype it is bound to. Histamine receptors H1–H4 are widespread throughout the body but there is limited knowledge about the H4R. The role of H4R in neuropathic pain transmission and other diseases is still controversial after nearly 20 years since its discovery. This may be due to biased signaling of histamine and H4 receptor agonists and differential effects on multiple signaling pathways in central and peripheral parts of the sensory nervous system. However, in the last two decades, there was a particular increment in evidence supporting participation of H3R and H4R in neuropathic pain modulation [1]. Histamine has also been identified to be responsible for a vascular type headache, e.g., migraine, hence the antihistamines are regarded as a possible treatment [2]. The proper action of particular subtypes of histamine receptors is of special importance as it has been shown for instance for the delirium syndrome in which H1R and H2R antagonists have pro-delirium potential, while H3R antagonists have proved to be beneficial in combating delirium. The H4R may also play an indirect role requiring further intensive exploration [3].
Pulmonary fibrosis is the most frequent form of interstitial lung disease. Unavailability of effective therapies has led to the urge of exploiting novel curative approaches. Histamine receptor H₄ has been recognized as a new target for inflammatory and immune diseases, and H₄R ligands reduced inflammation and oxidative stress in lung tissue. It has been shown that poly(ADP-ribose) polymerase (PARP-1) and H₄R are both involved in inflammatory and fibrotic responses. Treatment with H₄R antagonist JNJ7777120 ((5-chloro-1H-indol-2-yl)(4-methyl-1-piperazinyl)-methanone; CAS Number 459168-41-3; Molecular Weight: 277.8) in a condition of PARP-1 inhibition, provides anti-inflammatory and anti-fibrotic effects, causing reduction in airway remodeling and bronchoconstriction. Its synergistic effect with selective PARP-1 inhibitors could be of potential use for the treatment of pulmonary fibrosis [4]. Viral infections can be important contributors to development of asthma and chronic obstructive pulmonary disease. Pulmonary fibrosis is the main factor leading to pulmonary dysfunction and quality of life decline in SARS survivors. Gaining a deeper understanding of the interaction between Coronaviruses and the innate immune system of the host may shed light on the development and persistence of inflammation in the lungs and can possibly reduce the risk of lung inflammation caused by CoVs [5].

2. The Histamine Receptors—Localization and Function

Histamine receptors, numbered in the order of their discovery H₁R-H₄R, are G protein-coupled receptors (GPCRs) that constitute the largest family of cell surface receptors in humans and play a key role in cellular signaling. In the central nervous system (CNS), the histaminergic system is mainly modulated by histamine, an inflammatory biogenic amine involved in wide range of pathophysiological effects through interaction with histamine GPCRs which belong to class A (rhodopsin-like) GPCRs. These GPCRs differ in localization and cellular signaling mechanisms and they even differ in the level of constitutive activity, i.e., the ability to adopt an active conformation independent of ligand binding [6,7]. H₁R and H₂R are found in the brain and periphery, H₃R is abundant in the CNS, while H₄R has low expression, if any, in the CNS and is predominantly expressed on a variety of peripheral immune cells such as eosinophils, dendritic cells, mast cells (HMC-1, LAD-2, and primary cord blood derived CD34+ human mast cells), leukocytes, and T-cells (including γδT, T helper 1, 2, Th17, and CD8 cells) [6,8–12]. The presence and role of H₄R in brain nervous tissue is yet elusive and not fully known but the presence of H₂R in non-neuronal cells in the brain has been confirmed [13,14]. Functional H₄ receptors that increase [³⁵S]-GTPγS binding and/or decrease noradrenaline release have not been identified in human, guinea pig, and mouse cortex [15]. In human mast cells, H₄R mediates release of cytokines, leukotrienes, and chemokines (TGF-β1, TNF-α, TNF-β, PDGF-BB, TIMP-2, M-CSF, IP-10, IL-16, IL-6, IL-3, IL-10, MIP-1α, IL-1α, ICAM-1, Eotaxin-2, RANTES, IL-8, MCP-1, and IL-6sR) [10].

Being a member of the most populated class A of the GPCR superfamily, human H₄R also contains seven transmembrane helices and a short amphipathic helix that possibly runs parallel to the cytosolic membrane surface. It consists of 390 amino acid residues possessing all of the highly conserved sequence motifs [16,17] of the class A GPCRs including the most evolutionary conserved residues in each of the transmembrane helices: N1.50, D2.50, R3.50, W4.50, P5.50, P6.50, and P7.50 (Ballesteros–Weinstein numbering [18]) indicating the same activation mechanism of H₄R as that of the other receptors in class A GPCRs [19]. The Ballesteros–Weinstein numbering scheme of GPCRs provides information about the relative positions of amino acids present in seven transmembrane helices. Each residue of the receptor is recognized by two numbers separated by a dot; the first number (1–7) indicates the number of the transmembrane helix where the residue is located while the second number indicates its position in relation to the most conserved residue, assigned number 50, of the same helix. The prominent residues such as D3.32 and W7.40, specific for amine-activated GPCRs, are also present in the H₄R [20]. It has been observed that the two agonists (histamine and OUP-16) exhibit complementary interactions with residues D3.32, E5.46, and T6.55, while the reference antagonist JNJ7777120 exhibits interactions with D3.32 and E5.46 only (Figure 1), implicating a differentiating role of T6.55 in ligand binding and receptor activation [21,22]. There are also striking complementarities
Additionally, various substituted histamine derivatives such as R-(α)-methylhistamine have significant H4R binding in addition to H3R [6]. Istyastono et al. have shown that the E5.46Q mutation impaired the binding strength of clobenpropit and its derivatives in both those receptors [26]. Moreover, the L5.39V and E5.46Q mutations resulted in a decrease of binding of the reported ligands to H4R. This finding emphasized the importance of the E5.46 residue which provides a crucial interaction with antagonists [27].

A plethora of studies have related the heterogenic and complex pharmacology of histamine receptors to various diseases: H1R to the allergic inflammation, anaphylaxis, and motion sickness 

Among the histamine receptors, H1R and H4R possess 40% amino acid identity in the transmembrane region and they recognize the same endogenous ligand that is histamine. Due to such similarity the crystal structure of H1R has been used by many researchers for building the homology models of H4R. However, there are substantial differences in histamine receptor binding sites. For instance, N4.57 in H4R is equivalent to W4.56, L5.39 to K5.39, E5.46 to N5.46, and Q7.42 to G7.42 in H1R. Additionally, the mutations of residues N4.57 and E5.46 resulted in significant alteration of inhibition constants of JNJ7777120 which was the first reported H4R antagonist [23] and the homology model of H4R featured two specific hydrogen bonds and ionic interactions of JNJ7777120 to D3.32 and E5.46 [24]. H4R has the highest sequence homology with H3R as it possesses 37% amino acid identity in protein sequence and 58% identity in the transmembrane region. It is evident that a number of ligands of H4R also have a high affinity for H3R due to the identical amino acids within the binding site of both receptors, including E5.46, Y3.33, and Y6.51, involved in ligand binding [25]. These amino acids residues contribute to the similarity between the binding sites of hH3R and hH4R forcing similar conformations of ligands. This explains the number of ligands which are antagonists of both receptors. Additionally, various substituted histamine derivatives such as R-(α) cyanahistamine, R-(-)cyanahistamine, R-(-)dimethylhistamine and R-(-)-methylhistamine have significant H4R binding in addition to H3R [6]. Istyastono et al. have shown that the E5.46Q mutation impaired the binding strength of clobenpropit and its derivatives in both those receptors [26]. Moreover, the L5.39V and E5.46Q mutations resulted in a decrease of binding of the reported ligands to H4R. This finding emphasized the importance of the E5.46 residue which provides a crucial interaction with antagonists [27].

A plethora of studies have related the heterogenic and complex pharmacology of histamine receptors to various diseases: H3R to the allergic inflammation, anaphylaxis, and motion

Figure 1. The homology model of H4R with docked JNJ7777120 antagonist. The specific ligand–receptor interactions are shown on the right panel. D3.32 forms both a hydrogen bond and an ionic interaction with the charged amine group of the ligand.
sickness [28,29], H₂R to the stimulation of gastric acid secretion leading to peptic ulcer, GERD and aspiration pneumonitis [30,31], H₃R to the neurotransmission controlling sleep, cognitive processes, schizophrenia, epilepsy, and pain [32–37], and H₄R to the immune responses (cancers, myocarditis) and inflammation [38–42] (Figure 2). The H₃ and H₄ receptors have relatively high affinity for histamine (5–10 nM) compared to the low affinity of H₁R and H₂R which is in the μM range [6,43]. Hence, the biological response has been linked directly with the local tissue histamine concentration and functional expression of different receptors [6].

![Figure 2. Classification of histamine receptors (H₁R–H₄R) in relation to their functions. H₁R–H₃R transduce extracellular signals via Gα₁₁, Gα₁₆, and Gα₂₆ respectively, while H₄R acts through Gα₁₂, and β-arrestin. H₁R and H₂R are low-affinity receptors while H₃R and H₄R are high-affinity receptors towards histamine. Ligands of H₁R–H₄R have therapeutic applications in allergic inflammation, gastric acid secretion, neurotransmission, and immunomodulation, respectively. The information in the figure is partially based on [44].](image)

3. Species Differences of H₄R

Following the identification of the human H₄R (UniProt id: Q9H3N8), various sequences of mouse, rat, guinea pig, pig, dog, and monkey H₄R have been reported and functionally expressed [38]. Eighty-five protein sequences of H₄R orthologues from different species have been extracted from the UniProt database and aligned to draw the phylogenetic relationship between H₄R orthologues (Scheme 1). The H₄ receptors of the chimpanzee, gorilla, and orangutan show the highest sequence homology (98–99%) with the human orthologue (hH₄R). H₄ receptors of some species are highly homologous to hH₄R with sequence homology between 78% and 94%, specifically those of macaques, baboon, drill, Angolan colobus, mangabey, Cebus capucinus imitator, marmoset, and Philippine tarsier (Table 1). Orthologues in some species were only moderately homologous to hH₄R with sequence homology between 54% and 73% while the least homologous showed homology ranging from 10% to 47%. Pig, mouse, smooth cauliflower coral, Japanese scallop, turbot, and pig have each two H₂R orthologues while sea cucumber has three orthologues. However, these orthologues, show only 10–36% homology to hH₂R while all others show a substantially higher homology (>50%). As some of the sequences are still incomplete, changes in the phylogenetic tree are to be expected. Within these GPCR sequences, the typical aminergic GPCR features (D3.32 in TM3 and E5.46 in TM5) can often be
found. Detailed analysis of most of these species variants is however lacking even though it could provide useful tools to dissect receptor–ligand binding. Using site-directed mutagenesis Wifling et al. have proved that the F169, located in the second extracellular loop ECL2, is a crucial amino acid for differential interactions, affinities, and potencies of certain agonists with the human and mouse H₄R orthologues [45]. Receptor sequence differences have implications even for ligand function as the JNJ7777120 ligand acts as a partial inverse agonist at the human H₄R, but as a partial agonist at the rat and mouse H₄R which possess lower constitutive activity than their human counterpart. Therefore, differences in pharmacological activities of H₄R ligands between different species might hamper preclinical development of future H₄R drugs [46].

**Scheme 1.** Phylogenetic tree of H₄R orthologues. The sequences were obtained from UniProt [47] and the sequences were aligned with ClustalW and the cladogram was created with Clustal Omega service [48].
Table 1. Sequence similarities of species specific H4R to the human orthologue.

| Species                        | Scientific Name                  | UniProt ID     | Similarity to hH4R |
|--------------------------------|----------------------------------|----------------|-------------------|
| 1 Human                        | Homo sapiens                     | Q9H1N8         | 99%               |
| 2 Chimpanzee                   | Pan troglodytes                  | HEQED2         | 98%               |
| 3 Gorilla                      | Gorilla                          | G3QS38         | 98%               |
| 4 Pygmy chimpanzee             | Pan paniscus                     | A0A2IR9QY6     | 98%               |
| 5 Orangutan                    | Pongo abelii                     | HE2ZW7         | 98%               |
| 6 Crab-eating macaque          | Macaca fascicularis             | Q8W9C8         | 94%               |
| 7 Pig-tailed macaque           | Macaca nemestrina                | A0A2KD1G7      | 94%               |
| 8 Rhesus macaque               | Macaca mulatta                   | G7NH19         | 94%               |
| 9 Olive baboon                 | Papio anubis                     | A0A066CN9      | 94%               |
| 10 Drill                       | Mandrillus leucophaeus           | A0A2SKYBZ5     | 94%               |
| 11 Angolan colobus             | Colobus angolensis palliatus     | A0A2K3HHL6     | 93%               |
| 12 Sooty mangabey              | Cercocerus atys                   | A0A2K5Q7LQ7    | 93%               |
| 13 Black snub-based monkey     | Rhinopithecus bieti              | A0A2KD1G7      | 93%               |
| 14 Golden snub-based monkey    | Rhinopithecus roxellana          | A0A2SKYBZ5     | 93%               |
| 15 White-tufted ear marmoset   | Callithrix jacchus               | F8TJ13         | 93%               |
| 16 Olive baboon                | Aotus nancymaa                   | A0A3Q7WBT8     | 93%               |
| 17 Cebus capucinus             | Colobus angolensis palliatus     | A0A2K3HHL6     | 93%               |
| 18 Dog                          | Canis lupus familiaris           | J9P1C3         | 91%               |
| 19 Golden hamster              | Mesocricetus auratus             | A0A2Q7Q7T1     | 91%               |
| 20 Grizzly bear                | Ursus arctos horribilis          | A0A3Q7WBT8     | 91%               |
| 21 Small-eared galago          | Otocolobus alleni               | P11315         | 91%               |
| 22 Thirteen-lined ground squirrel | Lipotomys tridecemlineatus   | IMCG71         | 91%               |
| 23 Elephant                    | Loxodonta africana               | G3STF1         | 69%               |
| 24 Chinese hamster             | Rhinopithecus roxellana          | A0A2SKYBZ5     | 69%               |
| 25 Horse                       | Equus caballus                   | F6Z8L3         | 69%               |
| 26 Hedgehog                    | Erinaceus europaeus              | A0A2Y9GRV4     | 69%               |
| 27 European domestic ferret    | Mustela putorius                 | M3Y4H4         | 69%               |
| 28 Pig                         | Sus scrofa                       | Q8WNY9(Pig 1)  | 67%               |
| 29 Red fox                     | Vulpes vulpes                    | A0A3Q7SYT7     | 67%               |
| 30 Black flying fox            | Pteropus alecto                  | L5K5C7         | 67%               |
| 31 African elephant            | Loxodonta africana               | G3STF1         | 67%               |
| 32 Giant panda                 | Ailuropoda melanoleuca           | G1M6D3         | 67%               |
| 33 Asian elephant              | Ailuropoda melanoleuca           | G1M6D3         | 67%               |
| 34 American mink               | Neovison vison                   | A0A452Q6Z      | 67%               |
| 35 Sperm whale                 | Odobenus rosmarus divergens      | A0A2KD1G7      | 67%               |
| 36 Dog                          | Canis lupus familiaris           | J9P1C3         | 67%               |
| 37 Rabbit                      | Orctolagus cuniculus             | G1M6D3         | 67%               |
| 38 Rat                          | Rattus norvegicus                | Q91ZY1         | 67%               |
| 39 Red fox                     | Vulpes vulpes                    | A0A3Q7SYT7     | 67%               |
| 40 Black flying fox            | Pteropus alecto                  | L5K5C7         | 67%               |
| 41 Kangaroo rat                | Dipodomys ordi                   | A0A1S3F27     | 67%               |
| 42 Hawaiian monk seal          | Neomomus schausiani              | A0A2Y9GRV4     | 67%               |
| 43 Giant panda                 | Ailuropoda melanoleuca           | G1M6D3         | 67%               |
| 44 Eastern chipmunk            | Tamias striatus                  | A0A2Y9GRV4     | 67%               |
| 45 Squirrel monkey             | Saimiri sciureti                 | A0A2Y9GRV4     | 67%               |
| 46 Dog                          | Canis lupus familiaris           | J9P1C3         | 67%               |
| 47 European domestic ferret    | Mustela putorius                 | M3Y4H4         | 67%               |
| 48 Mouse                       | Mus musculus                     | B2ZCH2(Mouse 2)| 67%               |
| 49 Goat                        | Capra hircus                     | A0A452DK10     | 67%               |
| 50 Sheep                       | Ovis aries                       | W5PBL0         | 67%               |
| 51 Black bear                  | Canis lupus familiaris           | J9P1C3         | 67%               |
| 52 Groundhog                   | Erinaceus europaeus              | A0A1S3F27     | 67%               |
| 53 Black bear                  | Canis lupus familiaris           | J9P1C3         | 67%               |
| 54 Yangtze river dolphin       | Lipotes vexillifer               | A0A2Y9GRV4     | 67%               |
| 55 American mink               | Saimiri sciureti                 | A0A2Y9GRV4     | 67%               |
| 56 Hybrid cattle               | Lipotes vexillifer               | A0A2Y9GRV4     | 67%               |
| 57 Black bear                  | Canis lupus familiaris           | J9P1C3         | 67%               |
| 58 Yangtze river dolphin       | Lipotes vexillifer               | A0A2Y9GRV4     | 67%               |
| 59 American mink               | Saimiri sciureti                 | A0A2Y9GRV4     | 67%               |
| 60 Yangtze river dolphin       | Lipotes vexillifer               | A0A2Y9GRV4     | 67%               |
| 61 American mink               | Saimiri sciureti                 | A0A2Y9GRV4     | 67%               |
| 62 Indio-pacific humpbacked dolphin | Saimiri sciureti            | A0A2Y9GRV4     | 67%               |
| 63 Narwhal                     | Monodon monoceros               | A0A452Q6Z      | 67%               |
| 64 Atlantic bottle-nosed dolphin | Tursiops truncatus           | A0A2U3Y3K5     | 67%               |
| 65 Gray short-tailed dolphin   | Monodelphis domestica           | F6G6B5         | 67%               |
| 66 South-Pacific minke whale   | Balaenoptera acutaenotnata sacmmoni | A0A252C640   | 67%               |
| 67 Tasmanian devil             | Sarcophilus harris              | G3X3P1         | 45%               |
| 68 Weddel seal                 | Leptonychotes weddelii           | A0A2U3Y3K5     | 42%               |
| 69 Atlantic bottle-nosed dolphin | Tursiops truncatus           | A0A2U3Y3K5     | 42%               |
| 70 White-tailed sea-eagle      | Haliaeetus albicilla             | A0A91N2C4     | 41%               |
| 71 Ibis                         | Apladneria citoitum              | A0A91N2C4     | 41%               |
| 72 American mink               | Saimiri sciureti                 | A0A2Y9GRV4     | 40%               |
| 73 Turbot                      | Scophthalmus maximus             | A0A2U9B2J1     | 40%               |
| 74 Atlantic bottle-nosed dolphin | Tursiops truncatus           | A0A2U3Y3K5     | 40%               |
4. The Pharmacological Effects of H₄R Ligands

Although the pharmacology of H₄R ligands is yet not fully elucidated H₄R has been widely studied and reviewed since its characterization and cloning in 2000 [25,49]. The vast body of accumulating knowledge on physiological and pathophysiological functions associated with H₄R modulation can be exploited for therapeutic purposes [11]. The properties of H₄R make this amine receptor and its ligands of interest to specialists in the field of allergology, neurobiology, gastroenterology, endocrinology, and also to researchers of cardiovascular functions [6,50]. The results of research on the role of H₄R in various pathophysiological and immunological processes indicate its association with the development and course of many diseases including a crucial role of H₄R in airway and dermal inflammation (Figure 3), pruritus, ocular inflammation, arthritis, systemic lupus erythematosus, Sjogren’s syndrome, multiple sclerosis, gastric ulcer, cancer, and pain [12,51].
4.1. Allergic Diseases

Inflammatory conditions were for a long time thought to be mediated by activation of the histamine receptor subtype 1. However, the discovery and pharmacological characterization of H_{4}R ligands especially antagonists, (and, to a lesser extent H_{3}R and even H_{2}R ligands) on mast cells, eosinophils, and T cells demonstrates the possibility of its involvement in inflammatory conditions/symptoms such as atopic dermatitis (AD), asthma, allergic rhinitis, rheumatoid arthritis (RA), and pruritus in humans. This is evident from the results obtained in diverse experimental models of inflammation including hepatic ischemia-reperfusion, colitis, atopic dermatitis, in which H_{4}R antagonists (JNJ7777120, JNJ10191584, thioperamide) proved to be efficient anti-inflammatory agents with reduced neutrophil recruitment and release of cytokines [51,52]. Preclinical and clinical data strongly suggest the regulatory involvement of H_{4}R in the calcium influx and cellular chemotaxis [53,54], hence establishing a link between the potential therapeutic application of selectively acting H_{4}R ligands to inflammatory conditions while also indicating involvement of H_{4}R in diseases accompanied by itch and pain [55]. The investigations of histamine in the inflammation process have led to a development of the first highly potent and selective non-imidazole H_{4}R antagonist JNJ7777120, followed by reexamination and synthesis of a plethora of H_{4}R-targeted compounds [50,51].

Currently, many H_{4}R ligands are known, synthesized, and evaluated [56,57]. Studies using selective H_{4}R ligands in animal models of pruritus revealed a role for H_{4}R in mediating chronic pruritus associated with conditions such as atopic dermatitis [51,58]. Antagonists of H_{4}R (JNJ7777120, JNJ39758979, INCB38579, and others) reduced pruritus in a number of animal studies [59] as well as itching sensation in different conditions in human patients. Alcaftadine, a topical ophthalmic drug indicated for the prevention of itching associated with allergic conjunctivitis, is a potent H_{1}R and H_{2}R antagonist (in fact, inverse agonist) with weak inverse agonistic activity also towards H_{4}R [60]. Administration of H_{1}R/H_{4}R antagonists or co-administration of H_{1}R and H_{4}R antagonists will probably be effective also in humans. Such antagonists are more efficacious as compared to olopatadine (H_{1}R antagonist without H_{4}R activity) [61]. Consequently, these studies indicate that H_{4}R is involved in mediating pruritic responses in humans, and that H_{4}R antagonists are ought to be effective in the treatment of pruritic histamine-mediated conditions, such as AD, acute urticaria, allergic rhinitis, or allergic conjunctivitis.

The histamine receptor H_{4}R was also found on cartilage cells–chondrocytes [62,63]. As the presence of the histamine triggering protein (HRF) has been identified in the joints of people with RA, it seems very likely that H_{4}R antagonists will be used in the future in the treatment of RA [64]. This receptor may also be important in the pathogenesis of Sjögren’s syndrome, erythematosus lupus erythematosus, and atopic dermatitis [65]. H_{4}R activation not only results in phosphorylation of ERK and PI3K in a time dependent manner but it also leads to enhanced synthesis of inflammatory mediators associated with allergic reactions. It leads to inflammatory conditions as well as contributes to postinflammatory visceral hypersensitivity, thus, making H_{4}R antagonists important for reducing inflammation and normalizing postinflammatory visceral hypersensitivity [66].

4.2. Asthma

H_{4}R seems to be an interesting pharmacological target in the treatment of asthma [6]. Asthma is a condition typically characterized by involvement of eosinophils and mast cells [67–69]. Extensive studies have provided evidence detailing the functional profile of H_{4}R in eosinophil biology [70] and in the chemotaxis and differentiation of other immune cell types. In experiments carried out on animal models of inflammation of the airways, it was observed that in mice lacking the H_{4}R gene, there was a significant reduction in the allergic reaction caused by the administration of a chicken protein-ovalbumin [71]. Chemotaxis of eosinophils was shown to be blocked by H_{4}R selective antagonists (JNJ7777120, JNJ39758979, or JNJ10191584) in animal asthma models due to priming and T cell activation [51,72] while induced by histamine and selective H_{4}R agonists (e.g., 4-methylhistamine) [72]. Some selective H_{4}R antagonists in animal models of asthma proved beneficial
by mediating lung function and inflammation [51,73]. In asthma animal models, H4R antagonists act either directly by reducing the number of T cells at the site of inflammation [74] or indirectly when it is involved in dendritic cell function driving the response [51]. However, none of the H4R antagonists have been introduced to treat the above disorders.

4.3. Diabetes

The histamine receptor H4 may also be a therapeutic target in diseases not directly related to inflammation. For instance, H4R is suggested to be important in the pathogenesis of diabetes. In streptozotocin-induced diabetic rats H4R is overexpressed in tubular epithelial cells [75], and administration of a H4R antagonist resulted in a decreased blood sugar [76]. H4R participates in diabetic nephropathy progression through both a direct effect on tubular reabsorption and an indirect action on renal tissue architecture via inflammatory cell recruitment. Therefore, H4R antagonism emerges as a possible new multi-mechanism therapeutic approach to counteract development of diabetic nephropathy [77].

4.4. Parkinson’s and Alzheimer’s Diseases

Evidence about the H4R antagonist JNJ7777120 inhibiting propagation of microglial inflammation by attenuating the release of M1 microglial cells and largely preventing the pathological progression of Parkinson’s disease-like pathology and motor dysfunction has been provided by the latest research [78]. These findings support H4R as a promising novel therapeutic target for Parkinson’s disease. For Alzheimer’s disease the precise mechanism of histamine-induced Alzheimer’s pathology is not well known although the increased levels of histamine in plasma and in some areas of the brain are seen in Alzheimer’s dementia brain [79]. It is known that H3R can regulate cognitive and memory functions in the hippocampus so it could be involved in Alzheimer’s pathology [80]. Since H4R is also present in the brain and its stimulation regulates neuronal functions, then stimulating H4 receptors may have some beneficial effects in the brain of Alzheimer’s disease patients. Recently, it has been found that clobenpropit, a selective H3R antagonist with partial H4R agonist property, caused a significant reduction in amyloid-β deposits in a rat model of Alzheimer-like brain pathology. This effect was accompanied by marked reduction in neuronal or glial reactions so such dual-action compounds may have neuroprotective properties [81].

High similarity between H3R and H4R entails considerable similarity in ligand affinities and facilitates simultaneous activation of both receptors. Dual-acting H3R/H4R ligands may exhibit therapeutic potential in diverse pathological conditions, such as neuropathic pain, cancer, Parkinson’s, and inflammatory diseases [7,82]. Dual H3R/H4R imidazole containing ligands used so far includes compounds such as imetit, immepip, clobenpropit, and thioperamide [7].

4.5. Autoimmune Diseases

The characterization of a histamine receptor H4R with putative immunomodulating properties encouraged new hopes for the translational exploitation of this new therapeutic target for the still unmet medical needs, specifically asthma, autoimmune diseases, and a host defense. Rheumatoid arthritis (RA), which is a systemic autoimmune disorder, is characterized by chronic synovitis of peripheral joints, cartilage and bone destruction followed by joint disability. It was found that histamine and Th17 cytokines induced osteoclast differentiation from monocytes and JNJ7777120 decreased the osteoclastogenesis and the osteoclastogenic role of H4R has been evident in patients with RA [83]. Studies in the animal model of RA have shown that the H4R antagonist JNJ7777120 reduces the degree and severity of joint damage and reduces the number of cells producing IL-17 in the joint, thus, significantly inhibiting the inflammatory process in joints [84]. H4R involvement has been also confirmed in several types of cancers: melanoma [85], breast cancer [86], pancreatic cancer [87], and colorectal cancer [88]. H4R can regulate the aging and apoptosis of cancer cells and blocking H4R by antagonists inhibits tumor cell proliferation [86]. Histamine receptors play also an important role in
the pathogenesis of multiple sclerosis. It turned out that H1R and H2R play a propathogenic role while H3R and H4R may reduce the risk of the disease [89].

5. Clinical Trials of Drug Candidates Targeting H4R

Recently, H4R research has been gaining a lot of importance and the clinical studies were initiated for the putative therapeutic exploitation in inflammatory and allergic disorders [38] such as atopic dermatitis (AD) [59,90], pruritus, asthma, rheumatoid arthritis (RA), as well as in vestibular disease (Table 2) [91]. Toreforant (JNJ38518168), the first oral H4R antagonist, has been explored for the treatment of RA patients with active disease despite concomitant methotrexate therapy (phase 2 trials, ClinicalTrials.gov database entry NCT01862224 and dose range finding study NCT01679951) [92,93]. Both studies were prematurely terminated in 2014 because of the lack of efficacy. The similar phase 2 clinical studies for the same compound evaluating efficacy and safety of toreforant in patients with symptomatic uncontrolled, persistent eosinophilic asthma (NCT01823016) [94], and in patients with moderate to severe plaque-type psoriasis (NCT02295865) [95] were completed in 2015 and 2016. In the former study toreforant (at the dose tested) failed to provide any therapeutic benefit [96]. Preclinical toxicity studies of another H4R antagonist, JNJ39758979, provided sufficient evidence of an excellent safe profile encouraging the clinical level testing [72]. JNJ39758979 was observed to mitigate RA in the collagen-induced arthritis models (CIAM) [59]. The completed phase 2 clinical trial demonstrating its safety and effectiveness in human volunteers with persistent asthma (NCT00946569) whereas several phase 1 studies stating its safety and pharmacokinetics, as well as its effect on histamine-induced itch (pruritus) (NCT01068223) in healthy male volunteers have successfully been accomplished [97,98]. Simultaneously, the two phase 2 clinical studies were initiated to find a dose range of JNJ39758979 in patients with RA despite concomitant methotrexate therapy (NCT01480388) and patients with uncontrolled asthma (NCT01493882) but they were withdrawn in 2014 and 2015, respectively, due to the same reasons [99,100]. This adverse effect was predicted to be related with reactive metabolites of JNJ39758979 and not with H4R antagonism. Hence, the significant reduction in the pruritus after JNJ39758979 administration can be concluded in the way that drug-induced agranulocytosis can be most likely an off-target effect and other H4R antagonists could be beneficial in the treatment of AD, particularly pruritus, without serious adverse effects [101]. In the similar clinical studies, another oral, potent, and selective H4R antagonist ZPL3893787 has completed phase 2 clinical trials determining its safety, efficacy, and tolerability on pruritus in adult subjects with moderate to severe AD (NCT02424253) [102] and in patients with plaque psoriasis (NCT02618616) [103] in 2016 but no results for both these studies were posted on ClinicalTrials.gov. Results showed that ZPL3893787 improved inflammatory skin lesions in patients with AD, confirming H4R antagonism as a novel therapeutic option [90]. Additionally, in two different phase 2 trials, there is an evaluation safety and efficacy of ZPL3893787 in patients with moderate to severe AD (NCT03517566) [104] and the impact of its concomitant use along with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI) in patients with AD (NCT03948334) [105]. The efficacy of Seliforant (SENS-111) in patients suffering from acute unilateral vestibulopathy is currently under evaluation in Phase 2 trial (NCT03110458) [106]. The above-mentioned observations indicate a wide range of potential clinical applications of H4R ligands.
Conceptualization, P.M. (Pakhuri Mehta) and S.F.; writing—original draft preparation, P.M. (Pakhuri Mehta); writing—review and editing, P.M. (Pakhuri Mehta), P.M. (Przemyslaw Misztal), P.R., O.M., P.K. and S.F.; visualization, P.M. (Pakhuri Mehta); supervision, S.F.; funding acquisition, S.F., P.R. and O.M.

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