Chapter 7

Non-professional Histamine Producing Cells, Immune Responses and Autoimmunity

Yrjö T. Konttinen[1], Henrik Husu[1], Xia Han[1], M. Beatrice Passani[2], Clara Ballerini[3], Vasily Stegaev[1], Tarvo Sillat[1], Zygmunt Mackiewicz[4]

[1]Department of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland, e-mail: yrjo.konttinen@helsinki.fi

[2]Dipartimento di Farmacologia Preclinica e Clinica, Universita' di Firenze, Firenze, Italy

[3]Dipartimento di Scienze Neurologiche, Universita' di Firenze, Firenze, Italy

[4]State Research Institute Center of Innovative Medicine, Vilnius, Lithuania

Abstract

Histamine is a monovalent cationic biological amine synthesized by professional and non-professional histamine producing cells, which form two distinct cell categories. Professional cells produce, store and burst release their histamine from storage granules so that locally and temporarily for short periods high micromolar histamine concentrations are achieved. Non-professional cells generally produce and release histamine into the cytoplasm continuously without intermediated storage, to release it along its concentration gradient via histamine channels. These channels might play an important role in balancing, maintaining and regulating low-level histamine fluctuations, which tend to occur due to variation in the histamine content of the food, histamine production by microflora, histamine release from professional cells and enzymatic degradation and reuptake of histamine.

Effects of the professionally-produced high histamine levels are mediated via two low-affinity histamine receptors, H_1R and H_2R. In contrast, the non-professionally-produced, low nascent histamine levels are only able to activate two novel high-affinity histamine receptors, H_3R and H_4R. The former are active during short-term emergency "on-state" whereas the latter are active during a basic or long term homeostatic "off-state". Micromolar histamine/H_1R/H_2R amplifies expulsion of irritants (e.g. pollen, helminths) by adding to a direct irritant-induced

reaction an amplifying IgE-dependent immunological component. Nanomolar histamine/H_3R/H_4R seems to participate in dendritic cell-mediated antigen (Ag) presentation to T-cells in induction of self-tolerance, sensitization phase in allergy and delayed lymphocyte-mediated immune reactions. From this point of view, it is interesting that H_4R is best known for being expressed by myelopoietic cells, such as dendritic cells and lymphocytes, but also polymorphonuclear neutrophils, basophils, eosinophils and mast cells (MC).

The role of histamine has been mainly recognized during exacerbation of asthma, allergic rhinitis and conjunctivitis, urticaria and anaphylaxis as well as gastric acid secretion after a meal. Antihistamines are generally helpful during the acute stages of various allergic states associated with burst release of histamine. However, it seems that the basis of these conditions lies in a steadier underlying immune activity, e.g. Ag presentation by dendritic cells to T-cells and T-cell help to B-cell-dependent IgE immunoglobulin synthesis against T-cell-dependent Ag. Normally this system participates in the maintenance of health (immune tolerance and immune responses against pathogens), but in patients it can participate in the initiation and perpetuation of diseases and contributes to the recurrence of the symptoms and signs upon renewed exposure to the symptom triggers (allergens in allergies and auto-Ag in autoimmune diseases). Therefore, antihistamines or H_1R-antagonists and H_2R blockers provide limited therapeutic effectiveness in such conditions, but these conditions may in part be regulated by low histamine and high- affinity histamine receptors, in particular H_4R. Histamine H_4R modulation by small molecules administered perorally or locally might provide effective and affordable new remedies for various autoinflammatory, allergic and autoimmune diseases.

7.1. Introduction

Despite intense research efforts in the past, new observations on its fundamental function have recently been made regarding two intimately interrelated concepts, its non-professional synthesis and its novel high-affinity receptors.

The so-called "professional" histamine producing cells produce histamine rapidly in copious amounts and store it in storage granules, from which histamine and other granular contents can be rapidly released by exocytosis in a process that is generally regulated but sometimes apparently stochastic. "Non-professional" histamine producing cells generates histamine at a 100- to 1000-fold lower pace and release it directly to the cell cytoplasm without an intermediate storage stage. Thus, during the "off-state" they first produce histamine in the cytoplasm and then passively release it to the extracellular space along the concentration gradient, apparently at the same pace as it is produced. This histamine release is mediated by "equilibrative uniporter" histamine channels.

Apart from rapid, temporary and robust local histamine release or slow, low level constitutive histamine release, histamine uptake via these "equilibrative uniporters" is possible as well.

Extracellular burst-released micromolar histamine exerts it effects on histamine target cells via classical, low-affinity H_1R and H_2R receptors. In contrast, basal non-professional histamine exerts its effects directly only via high-affinity H_3R and H_4R receptors.

During MC activation and the high histamine "on-state", the classical histamine receptors are rapidly desensitized based on phenomena like receptor phosphorylation, G-protein uncoupling, receptor internalization and receptor gene transcription. At the same time, the numerous non-professional histamine producing cells assume an alternative histamine N-methyl transferase (HNMT)-depedent function as high-capacity histamine sinks, removing histamine effectively from the extracellular space for cytoplasmic degradation. These novel cells now work, not to maintain but to return back to the homeostatic nanomolar histamine concentrations. However, it is not clear how the histamine-sensitive, high-affinity histamine receptors cope with the excessive overstimulation during the local and temporary high histamine on-states.

7.2. Histamine

In human cells, histamine is synthesized from the essential amino acid (AA) L-histidine and this synthesis is dependent on L-histidine decarboxylase (HDC). Histamine release occurs either via exocytosis or passively via histamine channels. Exocytotic release is regulated and occur only after stimulation by allergens, substance P as well as other tachykinins, lectin-like structures, physical forces (mechanical stimulation) and various foodstuffs such as citrus fruit, strawberries and nuts (for a more complete list, see Maintz & Novak 1999). In addition, other food itemssuch as such as various fishes (mackerel, herring, sardine, tuna etc.), cheeses (Emmental, Swiss, Cheddar, Camembert) and alcohol (in particular red wine) also contain histamine. Human bodyis an ecosystem, which contains 10 times as many bacteria as it contains human cells, so the relase of histamine synthesized by intestinal bacterial flora can greatly contribute to physiological histamine concentrations. The latter source is notable because it suggests that HDC knockout mice are not "histamine-free".

7.2.1. Histamine Synthesis

It was traditionally thought that MC, basophils, enterochromaffin-like (ECL) cells and histaminergic neurons loaded with histamine-containing secretory granules were also responsible for histamine synthesis in the human body. It has since

been noted that histamine is an important immunomodulatory agent already at low nanomolar concentrations, and that leukocytes other than MC and basophils can also produce histamine, albeit at a much smaller scale. Furthermore, dendritic cells (DC), T-cells, monocyte/macrophages and neutrophils also produce histamine (Tanaka & Ichikawa 2011; Kubo & Nakano 1999; Szeberényi et al. 2001). Even non-immune cells such as fetal liver cells, ductal epithelial cells of the salivary glands, sperm cells, epithelial cells of the mammary glands and skeletal muscle cells can synthesize histamine. This suggests that histamine has numerous previously undiscovered physiological and pathological effects, apparently mediated by the recently discovered H_3R and H_4R receptors. Accordingly, it has been proposed that histamine can maintain homeostasis of salivary glands, stimulate neonatal hematopoiesis, regulate reproductive organs and improve adaptation of muscle cells to exercise (Tanaka & Ichikawa 2011; Niijima-Yaoita et al. 2012). Thus, the cells can be divided to two different categories: professional and non-professional histamine producing cells (Table7.1), which essentially utilize two different sets of receptors, secretory and intake pathways to regulate very different sets of bodily events.

The molecular basis of professional large scale histamine synthesis and non-professional small scale histamine synthesis as well as the differences between each process has been investigated, where at least two functionally relevant isoforms of HDC have been reported (Ichikawa et al. 2010; Tanaka & Ichikawa 2011). The full-length, low-activity 74-kDa HDC is in professional histamine producing cells proteolytically cleaved to a 53-kDa isoform, which is 100-1000-fold more active than its full-length precursor. In non-professional histamine producing cells the full-length post-translational 74 kDa isoform with a low enzymatic activity produces histamine to the cell cytoplasm (Tanaka & Ichikawa 2011; Kubo & Nakano 1999). The activity of this low activity HDC in non-professional, low scale histamine producing cells is not particularly stable in this transformation, but is known to be regulated at the transciptional and protein levels by various cytokines, including IL-1, IL-3, IL-12, IL-18, GM-CSF and TNF-α (Jutel et al. 2009). HDC activity changes in various infections, inflammation and the rejection of transplanted organs.

7.2.2. Histamine Release

Professional histamine producing cells store histamine in cytoplasmic secretory granules. Histamine in these granules is stored by ionic linkage to the carboxyl groups of proteins and heparin. A murine connective tissue MC contains 10-30 pg histamine per cell compared to < 0.2 pg histamine per cell in a mucosal MC. If 110 pg/ml of histamine is equivalent to 1 nM, it can be calculated that ~18500 connective tissue MCs could release enough histamine to 1 mL to reach 50 µM. Given that 10^4-10^5 MCs can be isolated from one gram of human tissues,

Table 7.1
Comparison of non-professional and professional histamine (HA) producing cells.

Property	Non-professional cells	Professional-cells
Rate of HA synthesis	Slow	100-1000 times faster
HA synthesizing enzyme	74-kD HDC	53-kD HDC
Handling of synthesized HA	Released to the cytoplasm	Stored in secretory granules
Requirement for release	Concentration gradient, need to overcome the resting cell membrane potential	Stimulus required[1]
Release of HA	Passively along the concentration gradient via equilibrative uniporters[2]	Actively via exocytosis
HA concentrations attained	Nanomolar	Micromolar
Concentration range	Probably very narrow	First very high, then rapidly falling off
HA concentration modulation in the active concentration range	HA from food and microbes	Burst release from professional cells
Spatial range	Universally present in the body	Usually local, at the hot spot
Time range	Long-term	Short-term
Active during	"Off-state" (most of the time)	"On-state" (short bursts)
Receptors utilized	High affinity H_3R, H_4R	Low affinity H_1R, H_2R (H_3R, H_4R)
Handling of extracellular HA excess	Degradation by DAO[3],uptake via equilibrative uniporters[1]	Degradation by DAO[3], uptake via equilibrative uniporters[1]
Handling of HA taken up	Degradation by HNMT[4]	Reuptake to granules by VMAT[5]

[1]Mechanical, HA releasing foods, lectins, substance P and other tachykinins, allergens (acting on IgE-sensitized cells)
[2]Organic cation transporter 2 (OCT2, SLC22A2), organic cation transporter 3 (OCT3, SLC22A3), plasma membrane-associated monoamine transporter (PMAT, SLC29A3, equilibrative nucleoside transporter 3/ENT3) are potential candidates
[3]Diamine oxidase
[4]Histamine N-methyl transferase
[5]Vesicular monoamine transporter 2

MCs can have the capacity to produce micromolar histamine concentrations in tissues. However, even in optimally timed plasma samples from patients with anaphylaxis, histamine levels may be within normal limits (Simons et al. 2008). At present, there is lack of technological *in vivo* histamine sensors which could continuously follow locally histamine concentrations in human tissues. Histamine burst by exocytosis release can be triggered bysuch as neuropeptides, some food items, helminths, mechanical stimulation, wounding or allergic reactions. It can lead to micromolar histamine concentrations, as estimated through the pK_i values of H_1R (4.2) and H_2R (4.3), of up to 50-100 μM (Lim et al. 2005), although the local and temporary nature of professional histamine release and

its subsequent rapid degradation and dilution are reflected in the relatively low 0.6 μM concentration measured in bronchoalveolar lavage fluid after Ag challenge (Calhoun et al. 1998).

Non-professional histamine producing cells produce and secrete 100- to 1000-fold lower concentrations of histamine and their histamine release (or uptake) is mainly driven along the concentration gradient between the intra- and extracellular space (Jutel et al. 2009; Tanaka & Ichikawa 2011; Kubo & Nakano 1999). Effective concentrations at this low histamine level are nanomolar, again mainly estimated through the pK_i values of H_3R (8.0) and H_4R (8.2).

7.2.3. Histamine Receptors in General

Histamine affects cells via four histamine receptors which all belong to the large G-protein-coupled receptor (GPCR) family. These receptors contain extracellular, transmembrane and intracellular domains where the ligand-binding structures are located on the extracellular part of the receptor molecule. The intracellular domain of the receptor binds various G-proteins which are dependent on the receptor and cell type. Thus, G-proteins mediate the extracellular signals affecting the extracellular part of the receptor intracellularly via downstream activation and/or inhibition of various intracellular signal transduction cascades. This ultimately leads to various rapid events such as release of intracellular calcium stores and the phosphorylation ordephosphorylation of proteins as well as additional slow changes in gene transcription events.

7.2.3.1. Histamine H_1 receptors

Although the first antihistamines, were regularly used by the 1940s, it took until 1966 before Ash *et al.* introduced the term H_1R to describe a subgroup of histamine sensitive receptors which could be blocked by the first generation antihistamines or H_1R-antagonists (Ash & Schild 1966). Since H_1R-antagonists only inhibited some of the histamine effects, such as contraction of the smooth muscle but did not affect some others, like production of gastric acid, led the authors to the conclusion that the effects of histamine must be mediated by at least two different receptors. On the other hand, many of the so called antihistamines also inhibit muscarinic, α-adrenergic and serotonin receptors and modulate ion channels, which is reflected insuch as adverse effects such as dry mouth and other anticholinergic effects, orthostatic hypotension, increased appetite and arrhythmias, like torsades de pointes.

H_1R is best known for its localization on the vascular endothelial and smooth muscle cells, whereas the best known localization of H_2R is on the parietal cells of the stomach. High concentrations of histamine are already known to be responsible for vasodilation, increased vascular permeability,

the expression of adhesion molecules on vascular endothelial cells, contraction of the bronchial smooth muscle, stimulation of gastric acid production, neurotransmission in the central nervous system (CNS) and even modulation of immune-inflammatory responses via esosinophils, basophils, neutrophils/macrophages, MC, DC, T- and B-lymphocytes (Akdis & Blase 2003; Simons 1999; Haas et al. 2008; Huang & Thurmond 2008 ; Feng et al. 2013). Many of these already known histamine effects are rather acute and are apparently mediated by the classical H_1R and H_2R, where the requisite, high histamine concentrations are only achievable transiently following regulated, professional burst release. High-affinity H_3R and H_4R react to basal histamine concentrations, which are only 1/1000 – 1/10000 of the concentrations effectively activating H_1R and H_2R.

H_1R mRNA is encoded by HRH1 gene in chromosome 3p25. The H_1R protein is composed of 487 amino acids (de Backer et al. 1998). H_1R is coupled via $G_{q/11}$ protein to activation of phospholipase C (PLC). This produces 1,4,5-inositoltrisphosphate (IP_3) and 1,2-diacylglycerol (DAG), which cause calcium (Ca^{2+}) mobilization from intracellular stores and activation of Ca^{2+} and/or DAG-dependent protein kinase C molecules. H_1R activation can also activate phospholipase A_2 (which releases arachidonic acid from membrane phospholipids), phospholipase D (which releases phosphatidic acid from phospholipids) and transcription factor Nuclear Factor kappa K (NFκB) (Leurs et al. 2002). Some of the H_1R on the cell surface membrane shows intrinsic (constitutive) activity without any histamine ligand binding, but the physiological consequences of this observation have not been clarified yet. Increased expression of H_1R has been noticed in several diseases, such as allergic rhinitis, rheumatoid arthritis (RA) and in some areas of the brain as a result of stroke.

Histamine promotes inflammatory responses and cytokines and some of these effects are mediated via H_1R (Dy & Schneider 2004). H_1R-antagonists, have shown effectiveness in the treatment of allergic rhinitis, conjunctivitis and skin reactions caused by exposure to allergens. CNS-related side effects, in particular sedation, have limited the use of the lipophilic first generation H_1R-antagonists. More modern second generation H_1R-antagonists are more hydrophilic molecules so their penetration through the blood-brain-barrier (BBB) and sedative effects are much smaller. Sedative side effects have been used in the treatment of allergic diseases associated with sleep disturbances. Cardiomyocytes express H_1R and therefore H_1R-antagonists could affect heart muscle and function, nevertheless no cardiotoxic effects have been described by the second generation H_1R-antagonists (Simons 2004).

By and large, H_1R activation seems to increase Ag presentation and costimulation to induce Th1/M_1 type of immune responses, associated with e.g. IL-12 and IFN-γ production, at the same time when it is blocking humoral immunity and IgE production (Simons 2004).

7.2.3.2. Histamine H_2 Receptors

In the 1980s, the introduction of H_2R-antagonists into the clinic revolutionized the treatment of gastric and duodenal ulcer and gastro-esophageal reflux disease (GERD). Because H_2R-antagonists strongly inhibited the production of gastric acid ("no acid, no ulcer"), the earlier, mainly surgical treatments, like pyloroplasty or Billroth I or II type gastric resections, without or with vagotomy, were rapidly abandoned.

The H_2R is coded by HRH2 gene in 5q35.2 and the corresponding protein is composed of 359 amino acids (Traiffort et al. 1995) (Entrez Gene, HRH2). The H_2R is coupled to $G_{\alpha s}$-type G-protein. Binding of agonist to H_2R stimulates adenylate cyclase, cAMP, protein kinase A (PKA) and cAMP response element-binding protein (CREB), modifying both phosphorylation and more slowly gene transcription. Activation of H_2R stimulates c-Fos, c-Jun (which together form the activating protein-1 (AP-1) transcription factor), protein kinase C and p70S6kinase (Dy & Schneider 2004; Jutel et al. 2009).

H_2R is found on parietal cells, but also on epithelial cells, endothelial cells, smooth muscles cells surrounding blood vessels, bronchiole, stomach and bowel, neurons, cardiomyocytes and cells of the immune system (neutrophils, eosinophils, monocyte/macrophages, DC, T- and B-lymphocytes). In the CNS, H_2R is a postsynaptic receptor often occurring in the same locations as H_1R, which may have synergistic effects between them (Haas et al. 2008). H_2R knockout mice display impairment of cognitive functions and changed nociception. In contrast to H_1R activation, H_2R activation diminishes eosinophil and neutrophil chemotaxis (Simons 2004). H_2R-agonism diminishes production of IL-12 by monocyte-derived DCs (MoDC), where the cytokine polarizes T_h0 to Th1 cells, but this diminished IL-12 production can be prevented by H_4R agonists (Gutzmer et al. 2005). Thus, H_2R-activation seems to downregulate Th1/M_1-type cell-mediated immuno-inflammatory responses and support Th2-inducing DCs and humoral immunity (Simons 2004).

Physiological effects mediated by H_2R include relaxation of the smooth muscle layer of blood vessels, increased vascular permeability, increased production of mucus and bronchodilation, and positive chrono- and inotropic effects on the heart (Simons 2004). CNS-effects are uncommon, perhaps in part because H_2R-antagonists are not lipophilic and do therefore not easily penetrate the BBB.

In 1975, Clark *et al.* discovered that low concentrations of histamine are chemotactic to eosinophils, whereas high histamine concentrations inhibit eosinophil chemotaxis, allowing them to participate in allergic inflammatory processes (Clark et al. 1975). After the discovery of H_4R, which has a very high affinity for histamine, it has been shown that low, 10-100 nM histamine concentrations cause changes in the form of the cell, upregulation of adhesion

molecules (CD11b) and polymerization of the actin cytoskeleton via H_4R (Buckland et al. 2003; Ling et al. 2004; Barnard et al. 2008). The low, nascent histamine concentrations that are generated and modulated by non-professional histamine synthesis have been shown to cause maturation of the secretory granules of MC, migration of MC and immunomodulation of DC, monocytes/macrophages, Kuppfer cells and basophils (Ichikawa & Sugimoto 2010).

The high-affinity receptors can therefore be proposed to mediate the effects of low concentrations of histamine, such as far away from the acutely inflamed hot spots (or around it), where they can downregulate inflammation, at the same time as the histamine concentration gradient acts as a chemotactic stimulus attracting leukocytes to the site of ongoing inflammation. Perhaps even more importantly, the high-affinity receptors can be proposed to mediate important processes in between the histamine burst releases when influenced by the non-professionally produced, low nanomolar nascent histamine fluctuating concentrations or modulated by food-derived or microbially-produced histamine. It is not yet known how high micromolar histamine concentrations affect the highly sensitive histamine sensors H_3R and H_4R, which are already stimulated by nanomolar histamine concentrations and/or to a large extent spontaneously active.

Histamine can also bind to non-conventional proteins, such as some enzymes of the cytochrome P450 superfamily, histamine transporters and proteins secreted by some insects, like nitrophorins and lipocalins (Dy & Schneider 2004). Lipocalins are highly specific histamine binding proteins, which are secreted by different types of ticks such as the hard tick (Ixodidae) and probably help the ticks to resist tick-bite-induced, locally-elicited host responses (Paesen et al. 1999).

7.2.3.3. Histamine H_3 Receptors

H_3R (Lovenberg et al. 1999) is encoded by HRH3 gene in 20q13.33 (Tardivel-Lacombe et al. 2001). H_3R protein is composed of 445 amino acids, but over 20 different isoforms are known (Cogé et al. 2001; Wellendorph et al. 2002; Wiedemann et al. 2002; Hancock et al. 2003), which suggests tissue, cell and context-dependent fine tuning in ligand binding and signal transduction.

One prominent H_3R location is on the histaminergic neurons in the CNS and in peripheral nervous tissues. In the CNS, H_3R acts as a presynaptic autoreceptor, where its activation inhibits neuronal histamine release (Haas et al. 2008; Passani & Blandina 2011). H_3R also occurs as a presynaptic receptor on other non-histaminergic neurons, where they are referred to as a heteroreceptor. In these cells, H_3R activation also inhibits the release of the corresponding neurotransmitters, such as acetylcholine, gamma-aminobutyric acid (GABA) and glutamate. All histaminergic CNS neurons, about 64,000 in

the human body, originate from the tuberomamillary nucleus, from which their axons pass to most other parts of the brain. Additionally, histamine released from the vagal complex of the *nucleus tractus solitarii* can probably modulate immune responses via H_3R (Haas et al. 2008).

H_3R is coupled to the $G_{i/o}$ protein (Cogé et al. 2001; Bakker 2004; Leurs et al. 2005), which inhibits adenylate cyclase, but H_3R activation can also activate mitogen-activated protein kinase (MAPK), increase intracellular calcium and activate phospholipase A_2.

Histamine in the CNS is associated with regulation of the sleep-wake state, ability to concentrate, learning and memory as well as other phenomena. It has therefore been natural to assume that H_3R-modulation could affect diseases which impair these functions, such as memory disorders in Alzheimer's disease, narcolepsy and attention deficit/hyperactivity disorder (ADHD). Additional hopes have been raised of its potential in the treatment neuropsychiatric diseases, such as schizophrenia.

H_3Rs are also found in the peripheral autonomic and somatosensory nerve terminals, which in turn can affect parasympathetic, sympathetic and sensory functions, such as pain and itch (4).

No drugs targeting mainly H_3R are at clinical use yet, but effects of H_3R inverse-agonists are studied in narcolepsy, sleep disturbances in Parkinson's disease, ADHD, schizophrenia and Alzheimer's disease as Phase II-III clinical studies (Passani & Blandina 2011). It is worthwhile to mention that betahistin, which is used in Ménière's disease, is a weak H_1R agonist, but a much more potent H_3R inverse agonist. It was originally thought that H_1R agonism relaxes pre-capillary sphincter muscles in small arterioles, thus improving the capillary circulation in cochlea (Ihler et al. 2012). Maybe the inverse agonist effect of H_3R autoreceptors on neurotransmitter release and afferent sensory signaling in the vestibular nucleus and cochlea are more important in diminishing vertigo in Ménière's disease (Desmadryl et al. 2012).

7.2.3.4. Histamine H_4 Receptors

H_4R (Oda et al. 2000; Liu et al. 2001; Morse et al. 2001; Nguyen et al. 2001; Zhu et al. 2001; Nakamura et al. 2002) is encoded by HRH4 gene 18q11.2 (Cogé et al. 2001). The full length H_4R is composed of 390 amino acids, but two non-signaling receptor isoforms have been identified, H_4(302 aa)R and H_4(67 aa)R (van Rijn et al., 2008). Co-expression of these different isoforms may participate in downregulation of the full-length H_4R on cell membrane, probably via receptor oligomerization. The amino acid sequence of H_4R has a 37 % homology with that of H_3R (58 % in the transmembrane region) (van Rijn et al. 2008). H_4R is coupled to the pertussis-toxin sensitive inhibitory $G_{i/o}$ protein (Gantner et al. 2002). The identification of JNJ-7777120 and other potent and selective H_4R

antagonists (Thurmond et al. 2008) made it possible to elucidate the roles of the H_4R in a variety of allergic and inflammatory processes.

Intracellular signal transduction of $G_{i/o}$-coupled H_4R occurs via inhibition of adenylate cyclase and lowered cAMP (Oda et al. 2000; Nakamura et al. 2000), increased phosphorylation of mitogen-activated protein kinase (MAPK) (Morse et al. 2001) and activation of PLC followed by increased cytosolic calcium and formation of DAG (Oda et al. 2000; Nguyen et al. 2001; Zhu et al. 2001). In a superficial way, the signal transduction cascades utilized by the novel H_3R and H_4R have resemblance, but this does not mean overlapping functions, because the cells and the cellular processes these receptors are coupled show wide variation. Due the common denominator of histamine for all histamine receptors known at present, combined with their generally prominent intrinsic activity, the system may maintain a rather complicated balance composed of interactions at the pre-, receptor- and post-receptor levels in cellular networks of various kinds (Nguyen et al. 2001; Xu et al. 2008; Hishinuma et al. 2010; Shi et al. 2012). This makes it difficult to extrapolate from simple *in vitro* experiments to human (patho)physiology.

H_4R has a relatively high intrinsic constitutive activity. In spite of this half-maximally active state, H_4R reacts to histamine concentrations as low as 5-10 nM (Thurmond et al. 2008; Jablonowski et al. 2003; Akdis & Simons 2006).

Expression of H_4R has been well described in haematopoietic cells. Both myeloid and lymphoid cells express H_4R, in particular eosinophils (Oda et al. 2000; Buckland et al. 2003; Ling et al. 2004; Barnard et al. 2008), MC (Hofstra et al. 2003; Lippert et al. 2004), DC (Zhu et al. 2001; Damaj et al. 2007; Geng et al. 2012), Langerhans cells (LC, dendritic cells in the epithelium of the skin and mucosa) (Gschwandtner et al. 2010), $CD4^+$ (Zhu et al. 2001; Sugata et al. 2007; Gutzmer et al. 2009) and $CD8^+$ T-cells (Zhu et al. 2001; Gantner et al. 2002), $CD16^+$ natural killer (NK) cells and CD1d-lipid complex binding invariant natural killer T-cells (iNKT) (Damaj et al. 2007; Leite-de-Moraes et al. 2009). H_4R but not H_3R is expressed on neutrophils (Oda et al. 2000; Zhu et al. 2001) and in experimental studies H_4R-agonism seems to mobilize neutrophils from the bone marrow (Takeshita et al. 2003, Takeshita et al. 2004). On the other hand, H_4R-agonism diminished monocyte-mediated production and secretion of CCL2 chemokine, also known as monocyte chemotactic protein-1 (Dijkstra et al. 2007). Low H_4R mRNA levels have been reported in B cells but the effects of receptor activation on B cells are not known yet (Zhu et al. 2001), although B_{reg} chemotaxis and IL-10 and/or TGF-β production to alleviate arthritis (Mauri et al. 2003), systemic lupus eryhtematosus (SLE) (Lenert et al. 2005), inflammatory bowel disease (IBD) (Mizoguchi et al. 2002) and experimental allergic encephalopathy (EAE) (Mann et al. 2007) by these cells is one possibility.

Except for immune cells, H_4R has been demonstrated thus far in skin fibroblasts and keratinocytes, fibroblast-like type B and macrophage-like

type A synovial lining cells and chondrocytes (Yamaura et al. 2013) as well as acinar and ductal epithelial cells in human salivary glands (Stegaev *et al.* 2012). Low and somewhat inconsistent expression of H_4R mRNA has been reported in osteoclasts, but no functional effects have been described (Biosse-Duplan et al. 2009). Expression of H_4R in neuronal cells has been a matter of debate, but more recent studies report H_4R in neurons of the nasal mucosa (Nakaya et al. 2004), primary vestibular neurons in rats (Desmadryl et al. 2012), neurons of the anterior horn of the spinal gray matter in mice (suggesting expression in motoneurons) (Lethbridge et al. 2010), in dorsal root ganglia in mice (suggesting expression in primary sensory neurons) (Kajihara et al. 2010), and in CNS in humans and rodents (Zhu et al. 2001; Connelly et al. 2009; Strakhova et al. 2009; Shan et al. 2012). H_4R-agonist 4-methylhistamine (4-MeHA) caused hyperpolarization of neurons of the somatosensory cortex in mice (Connelly et al. 2009). H_4R, together with H_1R and H_3R, has been reported in dorsal root ganglion of skin-specific sensory neurons in mice (Rossbach et al. 2011). H_4R stimulation led to an increase in cytosolic calcium. In experimental studies, H_4R-antagonist has an anti-pruritogenic effect, which could be due to a direct inhibition of the histamine-sensitive free nerve terminals in the skin (Thurmond et al. 2008). H_4R mRNA, again together with H_1R and H_3R mRNA, has been shown in human enteric neurons in the Meissner's submucosal neural network, where neurons were excited by H_4R stimulation (Breunig et al. 2007).

7.3. Histamine Transport

At physiological pH, histamine is a monocationic biogenic amine. Newly synthesized histamine is under homeostatic conditions released from the non-professional histamine producing cells either via OCT2 and 3, also known as solute carriers SLC22A2 and SLC22A3 respectively or PMAT, also known as solute carrier SLC29A3 or equilibrative nucleoside transporter 3, (ENT3).

After burst release of histamine, both professional and non-professional cells have an outside-in histamine gradient. Both utilize OCT2/3 (SLC22A2/SLC22A3) or PMAT (SLC29A3 or ENT3). PMAT transports other monoamines like serotonin and dopamine more effectively, with low affinity and high capacity. Equilibrative uniporters are not ATP-dependent active transporters, able to work against a concentration gradient, but let histamine and some other monovalent cations/biogenic amines pass along their concentration gradient. Histamine degranulation produces high histamine concentrations, perhaps up to 50 or even 100 μM. Part of the excessive histamine load is extracellularly degraded by diamineoxidase (DAO), which in general is considered to be responsible for 15-30% of total histamine degradation. Locally released histamine is rapidly diluted by diffusion and carried away by body fluids.

In cultured human HSG cells, 100 nM of radio-labelled histamine is enough to stimulate OCT3-mediated cellular uptake of histamine. On the other hand, after loading of these cells with 100 nM histamine, these cells release histamine from the cytoplasm to culture medium (Stegaev et al., 2013). This shows that OCT3 is functioning at rather low histamine concentrations, driven rather by the concentration gradient (and the negative resting cell membrane potential) than its high histamine affinity.

Extracellular *de novo* synthesized or dietary histamine can also be taken up by cells, which enables intracellular degradation (Duan & Wang 2010; Tanaka & Ichikawa 2011).

Both HDC isoforms are located on the endoplasmic reticulum, but only the 53-kDa HDC localizes close to intracellular granules, probably to facilitate their storage of the newly synthesized histamine via vesicular monoamine transporter 2 (VMAT-2) -mediated internalization (Tanaka & Ichikawa 2011).

7.4. Histamine Degradation

After burst release of histamine from both professional and non-professional cells, a steep outside-in downhill histamine gradient is formed. Both cell types utilize then the aforementioned histamine channels for cellular uptake, but differ in their handling of intracellular histamine. In professional histamine producing cells, some of the intracellular histamine is subjected to granular re-uptake via VMAT2 for recirculation. Apart from histamine synthesis and release by host and commensal microbial cells, as well as the histamine content of food, histamine concentrations in the body are dependent on the mostly extracellular DAO-mediated and intracellular HNMT-mediated histamine degradation processes mentioned above, which degrade histamine into imidazole acetate and N-methylhistamine, respectively. After cellular synthesis, DAO is initially located in vesicles located close to cell membranes, which upon stimulation release DAO into the extracellular space (Maintz & Novak 2007; Jutel et al. 2009). In mammals, DAO has been localized to the small intestine, ascending colon, placenta and kidneys. In renal tubular cells, DAO specifically localizes to the central clear matrix of the peroxisomes. Extracellular release of DAO and its activity in the extracellular space can be inhibited by various drugs, substances and alcohol. DAO-mediated extracellular degradation of histamine decreased in this way can increase histamine concentration and may cause histamine intolerance, depending on the individual and the context-dependent histamine response threshold (Maintz & Novak 2007). However, it is apparent that in the low nanomolar range levels of histamine concentration is continuously subjected to changes in the human body and sometimes peak to cause symptoms. In that respect, the basic non-professional histamine synthesis and intracellular degradation may exert important balancing ("buffering") effects on the cellular histamine micromilieu.

7.5. Constitutive Receptor Activity

H_4R has a high intrinsic constitutive activity meaning that it can exist in an active signaling state without a ligand bound to it. Normally ligand-free G protein-coupled receptor is in an inactive R state and assumes an active R* conformation (R*) first after binding its specific ligand, but intrinsically active receptors have assumed a similar activated H_4R^* state in the absence of a receptor-bound ligand (Milligan et al. 1995; Leff 1995). The constitutive or basal H_4R activity can therefore be described by the ratio between R* and R, and this basal activity is considered to be approximately 50% of the total H_4R activity. In spite of this half-maximally active state H_4R reacts already to histamine concentrations as low as 5-10 nM (Thurmond et al. 2008; Jablonowski et al. 2003; Akdis & Simons 2006). This relatively high constitutive activity may suggest that there is a low and potentially harmful threshold value below which the cells cannot go without damage, and to avoid such deprivation of histamine effects, a quite large pool of the receptors is maintained in an active transducing state even in the absence of any ligands.

Another important consequence of the constitutive receptor activities is that various receptor ligands can act as agonists, neutral antagonists or inverse agonists. Binding of natural or synthetic agonists favour the active conformation and subsequent signal transduction. Binding of a neutral antagonist to the receptor does not favour active or inactive receptor conformation alone and therefore does not by itself affect constitutive signalling. However, a neutral antagonist competes with an agonist for receptor binding, and therefore inhibits agonist-mediated receptor activation and signal transduction. Binding of inverse agonists (which earlier were also called antagonists) stabilizes and thus promotes the inactive receptor conformation, which leads to a shift of spontaneously active receptors to the inactive receptor pool and thus inhibits the constitutive receptor activity. This way, an inverse agonist diminishes the spontaneous receptor activity below the regular constitutive signalling level. All four histamine receptors have been shown to be generally constitutively active, but this is probably particularly important for H_3R and H_4R (Smit et al. 1995; Bakker et al. 2000; Morisset et al. 2000; Oda et al. 2000)., However, the importance of the balance between the H_1R-H_4R constitutive signalling pathways and the "off-state" and "on-state" function of various cells remains an interesting but open question.

7.6. Recognized Histamine-associated Diseases

Most known histamine-associated diseases in man seem to relate to enforced expulsion of micro- and macrostructures from the human body, such as pollen (~10-1000 µm) or parasitic worms (largest of which is broad tapeworm, which

grow usually 5-6 meters long, being then almost as long as the average human small intestine)(Pulendran & Artis, 2012). Pollen, eggs or larvae can intrude the human body via air (pollen via conjunctivae, nasal mucosa, airways), by mouth to the bowel and other internal organs (eggs ot tape worms etc.) or through the skin from where they can also reach the bowel and other internal organs (e.g. larvae in schistosomiasis). Many times they can be expelled, in part via burst released histamine triggered by lectin-like, MC activating structures (Imamura et al. 1996; Pramod et al. 2007), which is followed by tearing, sneezing, coughing or expulsion from the bowel. If the condition develops further, these reactions develop, like wound healing, to a robust type 2 rather than type 1 immune responses. This engages DC2, Th2 and M2 but for the initation of the type 2 response innate MCs and basophils and their cytokines such as IL-5 and IL-13 (later produced by Th2 cells together with IL-4) play important roles (Gordon 2003). Parasites participate actively in the induction of the host response by producing excretory/secretory products (proteinases, chitins) and egg Ag, which via danger receptors and T- and B cells receptors (TCR/BCR) interact with DC2, MCs, basophils, eosinophils, goblet cells, enterocytes, M2, Th2 and B cells (Wilson et al., 2007). In more chronic stages, the intruder can in part be isolated to granulomas, fibrosis and calcified cysts. One promising strategy in the treatment of these diseases is vaccination aiming to strengthen type 1 responses or immunotherapy aiming to induce Treg and suppression/tolerance, in which H_4R may plays a role.

Before the host response caused by direct irritation and naïve inflammatory responses e.g. of the airways, such as sneezing or coughing, can be strengthened by IgE-enhanced, MC- and basophil-mediated immediate-type I immune responses, the body must be sensitized. This engages DC-T-cell interactions, which are in part regulated by nanomolar histamine and H_3R and H_4R. If the body in spite of the initial non-immunological, irritative and naïve "get rid of the intruder"-type host responses cannot get rid of the intruder, its components are taken up and apart by the professional Ag-processing and -presenting DCs. Foreign Ag (linearized epitopes) are then in secondary lymphatic tissues presented in the context of major histocompatibility complex class II (MHC II) to TCR. For the T-cell to be activated by this Ag presentation, it needs also costimulatory signals, which are produced as a response to exogenous or endogenous (tissue damage) danger signals. Also B-cells present these Ag in the context of their surface MHC II to T-cells. If the Ag presenting B-cell recognizes an epitope of the same Ag in its soluble form by its surface immunoglobulin (*viz.* BCR, which was used to internalize the Ag in the first place), it becomes a plasma cell producing soluble antibodies. This is a joint result of the T-cell help, which provides co-stimulatory signals for the B-cell activation, and the Ag presentation to the B-cell via BCRs. In type 2 IL-4 and IL-13 driven response the immunoglobulin isotype switches from surface IgM and surface IgD to soluble IgE or IgG_4. This might in

part be related to the route of entrance of the irritatant immunological stimulus and its character. Sensitization and production of IgE help to expel the irritant even more effectively because the weaker and direct host responses are now enforced by an effective immunological activation of MCs and basophils. If this IgE production is local and the exposure only temporary, it could serve a useful purpose. However, if the IgE production is excessive, IgE spreads to more distant sites and the condition transforms to a disease-like and disturbing state known as allergy.

Thus, DC-lymphocyte interactions, sensitization and delayed T-cell-dependent immunological reactions related to H_3R and H_4R preceed the development of immediate, allergic repellent host responses related to H_1R and H_2R. It has long been known that this sequence is nicely depicted in reactions to mosquito bites (Mellanby 1946). Non-exposed and non-sensitized individuals do not produce any macroscopic skin response (stage I). After a number of mosquito bites the Ag dose is enough to lead to a delayed response apparent after one to several days after the bite (stage II). If the exposure to mosquito bites continues, an immediate response starts to develop to the bite in some 15 minutes and remains symptomatic for 1-2 hours (stage III). If the exposure to the salivary proteins released by the mosquito during its blood meal continues, the delayed-type response disappears and only the immediate-type response continues (stage IV); possibly as a result of development of inducible regulatory T-cells (iTreg) and blocking IgG_4. No more IgE antibodies are produced but some IgE still passively maintains the immediate type I reaction mode, a similar phenomenon as is seen in the Prausnitz-Küstner test. Upon further exposure, Ag-specific IgE diminishes and this leads to complete tolerance (stage V) so that in Lapps (Sami people) mosquito bites do not cause any response at all.

7.7. Immune Defence and Autoimmune Diseases

Self-tolerance fails severely in autoimmune diseases, which leads to cell and tissue pathology, patient symptoms and other clinical signs and findings ("horror autotoxicus").

According the clonal selection theory of immunity, central tolerance of the bone marrow-derived $CD4^-$, $CD8^-$ and TCR^- progenitor cells is established during their differentiation in the thymus. In cortical thymus, T-cell receptor gene rearrangement occurs followed by positive selection (clonal amplification) of properly finely-tuned lymphocytes, showing moderate self (MHC I or II) reactivity. T-cells showing overly weak reactivity against self-MHC molecules are subjected to negative selection via death by neglect, as they respond too weakly for their function even to Ag-loaded MHC complexes. Similarly, T-cells reacting too strongly against self-MHC antigens undergo activation-induced apoptosis, because they would be able to cause rejection of autologous tissue.

From the cortical thymus, $CD4^+$, $CD8^+$ double-positive T-cells pass to the thymic medulla, where they are now confronted with various self-Ag loaded to MHC, produced ectopically *in situ* as a result of molecules like AIRE (autoimmune regulator): very weakly reactive T cell clones die out of neglect, weakly self-reactive T cell clones can become conventional effector T cells (T_{eff}), moderately self-reactive and costimulated T cell clones with a quite wide TCR diversity become stable natural regulatory T cells (nT_{reg}; $CD4^+$, $CD25^+$, $Foxp3^+$ nT_{reg}) and strongly self-reactive T cell clones undergo activation induced apoptosis. Roughly 5% of the total T-cells subjected to clonal selection are then released as naïve T cells into the periphery. What is often forgotten is that the thymus undergoes involution after its peak development in puberty. Body is then largely dependent on the 10^8 T naïve cell clones produced, each clone consisting of 1000-10000 cells, depending on whether the total number of T cells is estimated to 10^{11} or 10^{12} (Arstila et al. 1999; Arstila et al. 2000). Interestingly, most of these T-cells never meet their specific antigenic determinant, as memory T-cells only make up < 1 % of the total cell diversity.

Due to various harmful events, such as trauma leading to a release of potential auto-Ag, it is also necessary to establish peripheral tolerance. This seems to be in part based on the danger signals. In the absence of danger signal-induced costimulatory factors, presentation of Ag alone leads to apoptosis of the lymphocyte (dying away), anergy of the lymphocyte (weaning away) or formation of $CD4^+$, $FoxP3^+$ inducible regulatory T cells (iT_{reg}, active resistance), preferably in the presence of a low dose of a high affinity antigenic determinant together with CD28 co-stimulation. iT_{reg} cells are important for example for tolerance against food Ag and commensal flora, where the development of these populations require a suitable cytokine milieu, in particular TGF-β (Yuan et al. 2012).

Anti-idiotypic responses also provide a means to control immune activation. All TCR and BCR contain highly variable but always clone-specificidiotopes, which are the structures responsible for the binding of epitopes (antigenic determinants). An oligoclonal, Ag-driven response defines a set of idiotopes, which is collectively referred to as an idiotype. For down-regulation of the immune response, anti-idiotypic TCRs and antibodies, representing "internal images" of the Ag, are produced. They bind to the antigen-specific TCR and BCR and can block Ag binding and responses. However, anti-idiotypic antibodies are not always restricted to blocking, as histamine burst release stimulating anti-idiotypic antibodies against IgE have been reported (Boutin et al. 1993).

The peripheral tolerance presented above is reactive, but it is also possible that some degree of proreactive autoimmunity is necessary for the maintenance of the immune balance. Self reactive lymphocyte clones could be maintained for active surveillance to recognize and respond to biomarkers, which reveal the site of the offence through tissue specific Ag, the type of the offence (cytokines, tissue damage induced inflammation, etc.) and the stress associated with it (stress proteins and the condition of the local cells) (Cohen 2007).

Because central selection is not 100% effective, autoimmunity could be based on *molecular mimicry* between microbial and self-Ag. Even in the absence of any initial cross-reactivity, a persistent infection can lead to *epitope spreading*, which reaches a point in the Ag where self-mimicking, cross-reactive epitope scripts are met. Professor Shunichi Shiozawa has introduced a model in which a persistent release of self-Ag even in the absence of infection (as a result of auto-Ag release upon exposure to UV light in SLE, for example) overstimulates the immune system so the *self-organized criticality* limit is surpassed, causing immune receptors to undergo *de novo* revisions leading to new reactivities which cover self-Ag (Tsumiyama et al. 2009). In *bystander activation* the antimicrobial response occurs in an infected and damaged tissue containing self-Ag in an environment invaded by mature and competent antigen presenting cells (APC) in a cytokine milieu favoring expression of co-stimulatory molecules. This leads to an immune attack against an innocent bystander self-Ag. Self-tolerance can be maintained by apoptosis which produces dominant tolerogenic antigenic determinants that only stimulate synthesis of anti-inflammatory cytokines. If this normal Ag processing is diverted as a result of tissue pathology, the very same Ag can instead produce *hidden (cryptic) immunogenic epitopes*, creating new self-derived molecules which lymphocytes did not meet during its education, eliciting an immune response.

7.8. Mast Cells and Autoimmunity

MCs are derived from the hematopoietic stem cells of the bone marrow, their precursors circulate in blood and they differentiate into granule-loaded "explosive" mature MCs in different tissues (Abraham & St. John 2010). In human tissues, tryptase-negative precursors or proliferation of MCs seem to be rare (Čeponis et al. 1998). Some tissue specificity in the final maturation is suggested by the dichotomy of MCs in rodents to mucosal MCs positive for mast cell tryptase and connective tissue MCs also positive for mast cell chymase. In contrast to murine MCs, human MCs do not produce IL-4 or express CD14 and IL-3R, FcγRI or functional TLR receptors are expressed in very small amounts, but they are strong IL-5 producers (Bischoff 2007). IL-5 stimulates B cell proliferation, increases immunoglobulin secretion and activates eosinophils.

MCs are best known for their role in immediate type I hypersensitivity reactions. IgE molecules with specificity against allergens like pollen) bind to MC surface FcεRI. When these sensitized MCs encounter allergens, cross-linking of the cell surface-bound IgE molecules leads to MC degranulation and activation. MCs can be stabilized by the drug sodium cromoglycate but also naturally by inducible OX40 on the surface of activated iT_{reg} cells, which interacts with OX40L on the MC surface (Mekori & Hershko 2012).

MCs contain also other preformed granular mediators like mast cell tryptase, heparin, IL-5, GM-CSF (granulocyte-monocyte colony stimulating factor), TNF-α, IL-17A and IL-17C. These cells can synthesize various eicosanoids as well as chemo- and cytokines. In a MC-dependent mouse model of zymosan-induced peritonitis, an H_4R-antagonist blocked neutrophil infiltration (Thurmond et al. 2004). Due to their role in DC maturation, polarization, migration, Ag presentation and other immunomodulatory processes, MCs participate in many autoimmune diseases, such as multiple sclerosis, bullous pemphigoid and RA, as demonstrated by lack of arthritis in MC-deficient mouse model and in RA by the improvement of type c-kit tyrosine kinase inhibitors (Eklund & Joensuu 2003).

MCs can produce IL-12 and IFN-γ, which can polarize D0, M0 and Th0 cells to type 1 cells; human MCs contain IL-5, both preformed and de novo produced, which can contribute to the polarization of other cells to type 2 cells; IL-6 and TGF-α, which can polarize cells to type 17 cells; and finally TGF- and IL-10, which can help polarize cells to T_{reg}. The outcome of the process to a large extent is context dependent. In particular, histamine decreased the production of poly I:C-induced, type 1 polarizing IL-12 by monocyte-derived DCs upon H_4R-agonist pretreatment (Gutzmer et al. 2005). Histamine at high concentrations also diminished lipypolysaccharide (LPS)-induced IL-12 production and promoted type 2 polarisation of DC and T_h0 cells via H_1R and H_2R (Caron et al. 2001; Kitawaki et al. 2006). MC can even present Ag to $CD4^+$ T-cells (Fox et al. 1994) and cross-present Ag to $CD8^+$ T-cells (Stelekati et al. 2009).

7.9. Dendritic Cells and Autoimmunity

H_4R mediates chemotaxis of human human myeloid DCs (Gutzmer et al. 2005). DCs are professional cells responsible for Ag sampling and surveillance. They capture (for which the outspread dendritic morphology is very suitable), transport (often through losing the dendritic morphology) and proteolytically process Ags and present it to T-cells after induced maturation, such as by danger signals, certain cytokines and immune complexes. DCs are often referred to as professional APCs, due to their critical role in primary immunization and sensitization, as no other cells are able to activate naïve T-cells (Steinman & Banchereau 2007). This functionality may depend on their capacity to migrate to secondary lymphoid tissue where they effectively interact with densily packed T-cells as interdigitating DCs in the paracortical T-cell area.

Ag presentation by DCs can result in induction of tolerance or immune activation. The two main categories of human DCs are conventional or myeloid $CD11c^+$, $CD123^-$ DCs (cDC or mDC, which can express TLR1-6 and TLR8) and plasmacytoid $CD11c^-$, $CD123^+$ DCs (pDC, naïve interferon type I-producing cells, characterized by TLR7 and TLR9) (Hashizume et al. 2005). CD11c is an integrin

α_x subunit, part of the Int $\alpha_x\beta_2$ complement receptor 4 for inactivated-C3b (iC3b), whereas CD123 is interleukin-3 receptor (IL-3R).

$CD11^+$ DC may have several subsets: $CD16^+$ DCs in blood, $CD1c^+$ ($BDCA\text{-}1^+$), which strongly expresses TLR4 and produces IL-10 and IDO in response to whole *E. coli* (Kassianos et al. 2012) and $CD141^+$ (BDCA-3), which strongly expresses TLR3 and effectively induces Th1 responses (Jongbloed et al. 2010).

DCs can also be classified as immature and mature, migratory (collecting Ags in the periphery as peripheral sentinels then migrating along lymphatic vessels to secondary lymphatic tissues to present them) and resident (possibly arising from blood-borne precursors or formed *in situ* in one lymphoid organ, where antigens are collected and presented in the organ before the cells undergo apoptosis) as well as non-polarized (DC_0) or polarized, where the latter is comprised of DC_1, which are produced by contact with stimuli such as bacteria including mycobacteria or poly I:C and induce a T_h0-to-Th1 shift by producing IL-12 and DC_2, which are produced by contact with stimuli such as helminths, thymic stromal lymphopoietin (also produced in epithelia) and PGE_2 and induce a T_h0-to-Th2 shift by producing IL-4 and other Th2 polarizing cytokines.

Both immature and mature DCs express H_1R, H_2R, H_3R and H_4R (Gutzmer et al. 2005; Jutel et al. 2009). DCs produced from human monocytes with GM-CSF and IL-4 belong to the non-professional histamine producing cells containing HDC and histamine, both of which increase up to 300-400% upon culture up to day 5. HDC inhibition as well as H_1R-antagonists and H_2R-antagonists decrease the DC differentiation-associated CD45 expression from day 3 by 60-80 % of control values. DPPE, inhibits histamine binding to microsomal and nuclear structures and downregulates CD40, CD86, CD33, HLA-DR and CD11c (Szeber nyi et al. 2001). Higher histamine concentrations achieved via MC degranulation exceed previously established peripheral tolerance via loss of T_{reg} suppression and lead to T-cell-mediated acute rejection of the skin graft (de Vries et al. 2009). However, this may relate to deprivation of tryptophan, another important MC product (Nowak et al. 2012).

Further support for the role of H_4R in the maturation of DCs, possibly via H_4R-agonism, has been obtained in asthma models. HDC knockout mice maintained on a histamine-free diet had reduced OVA-sensitized and challenged airway hyperreactivity, BALF eosinophilia, OVA allergen-specific IgE and late phase cytokine levels (Kozma et al. 2003). The questions are how much histamine was in these mice produced by the intestinal microbial flora and how important a role the constitutive activity of H_4R plays in this model. Histamine-binding tick protein given before OVA-Ag challenge effectively prevented murine OVA-induced allergic asthma associated bronchial hyperreactivity, peribronchial inflammation, pulmonary eosinophilia, mucus production and IL-4 and IL-5 secretion (Couillin et al. 2004). These histamine effects may be mediated via H_4R because H_4R knockout and H_4R-antagonist treated mice have decreased lung

inflammation and Th2 responses (Dunford et al. 2006). H_4R-agonism favours DC_2/Th2 responses, whereas lack of histamine and H_4R-antagonism diminish Th2 responses.

$CD1a^+$, $CD207^+$ (Langerin, a C-type lectin, which is a crucial component of Birbeck granules) Langerhans cells (LC) are perhaps the best known DC, residing in the epithelia of skin and mucosa LCs are monocyte/macrophage-derived DCs but seem to replenish to a large extent by local self-renewal. They belong to the so-called migratory DCs and can capture Ag by macropinocytosis, phagocytosis or receptor-mediated endocytosis after a local insult, leading to production of LC mobilizing TNF-α and IL-1β and then transport it to local lymph nodes. Once localized, LCs seem to participate in the maintenance of self-tolerance via activation, clonal proliferation and the maturation of iT_{reg} (Idoyaga et al. 2013). Interestingly, naïve T-cells seem to enter lymph nodes via high endothelial venules (HEV), whereas memory/effector T-cells enter mainly via afferent lymphatics (Förster et al. 2012).

Dermal cDCs residing in the upper dermis are composed of two subtypes: $CD1a^{high}$, $CD14^-$, $CD206^{high}$ and $CD1a^{low}$, $CD14^+$, $CD206^{low}$, CD209 (DC-SIGN) subsets, both of which express the coagulation factor XIII (Toebak et al. 2009; Chu et al. 2011). A special subtype of DCs, inflammatory dendritic epidermal cells (IDECs) are equipped with low- and high-affinity FcεRs (type II and I) and occur in skin lesions in atopic dermatitis. Cross-lining of the high affinity FcεRI IgE-receptor leads to IL-12 and IL-18 release, and Th1 polarisation. Th2-mediated inflammation with IL-4, IL-5 and IL-13 as well as IgE-driven MC degranulation prevail during the acute phase of atopic dermatitis, whereas eosinophils, macrophages and Th1 response with IFN-γ production are characteristic for the chronic phase with thickening of the epidermis and dermal fibrosis. IFN-γ increased H_4R on human monocyte-derived IDEC (Dijkstra et al. 2008).

Histamine can via H_2R stimulate endocytosis of Ag (Amaral et al. 2007). Regarding resident murine spleen DCs, histamine decreases their Ag presentation capacity in an apparently H_4R-mediated manner, as this effect was inhibited by a H_4R-antagonist and enhanced antigen presentation was observed in H_4R-/- DCs (Simon et al. 2011). After uptake of Ag, DCs can also pass them from the endocytotic compartment to the cell cytoplasm to be processed by the proteasome for cross-presentation of the antigenic epitopes in the context of MHC I. Cross-presentation is necessary for the mobilization of $CD8^+$ killer T-cells against malignant and virally infected cells if the DC themselves are not affected and would thus not be able to present tumour or viral Ags. Via H_3R and H_4R, histamine at low concentrations can stimulate cross-presentation of soluble but not particulate endocytosed Ags (Amaral et al. 2007). MHC I-restricted cross-presentation of self-Ag leads to induction of tolerance through deletion of autoreactive $CD8^+$ T-cells (Kurts et al. 1997). Therefore, it is possible that H_4R stimulation maintains production of tolerogenic DCs (tol-DC) during a steady

low histamine state, whereas adaptive immunity is raised against infections, which trigger DC-mediated production of IL-12 and IFN-α (Steinman et al. 2003). Activated DCs can rapidly recruit cells with a capacity to produce more cytokines, namely NK cells, which express H_4R (Damaj et al. 2007), and iNKT, in which H_4R is required to IL-4 and IFN-γ synthesis (Leite-de-Moraes et al. 2009).

DCs regulate the polarization of naïve $CD4^+$ T_h0 T-cells, which can be polarized to Th1 effector cells via IFN-γ and IL-12, producing IFN-γ, GM-CSF, CCR5 and CXCR3, to Th2 effector cells via IL-4, producing IL-4, IL-5, IL-13, CCR3 and CCR4, to Th17 effector cells via IL-6 and TGF-β, producing IL-6, IL-17, IL-22, CCR6 and IL23R, to T_{FH} cells via IL-6 and IL-27, together with interactions with follicular B cells or to iT_{reg} cells via IL-10 and TGF-β, producing IL-10, TGF-β and IL2R (Steinman & Banchereau 2007). Th1 and Th2 cells predominantly (but not exclusively) express H_1R and H_2R, respectively. H_4R deficient mice and mice treated with H_4R antagonist had decreased OVA-induced allergic lung inflammation and *ex vivo* induced T-cell-mediated IL-4, IL-5 and IL-13 production (Dunford et al. 2006).

H_4R expression has been shown on Th1, Th2 and Th17 cells (Mommert et al. 2011). Stimulation of H_4R on Th17 cells increased production of IL-17A and intracellular activation of activating protein-1 (AP-1) (Mommert et al. 2012). Th17 cells have been shown in psoriatic skin lesions and in acute atopic dermatitis. H_4R-agonists stimulate Th2 cells to produce IL-31, which causes itch (Mommert et al. 2011). This suggest that H_4R plays a role in the modulation of T-cells, which participate in the pathomechanisms of inflammatory skin diseases. Although we still lack detailed mechanistic studies, iNKT-cells have been associated with autoimmune diseases like primary biliary cirrhosis (PBC), psoriasis, MS, SS, SLE and RA (Simoni et al. 2013). In experimental PBC model, iNKT-cells play a key role in the initiation of the disease whereas iNKT-cells in other autoimmune diseases are supposed to play a stronger role during the chronic stages. These disease-promoting effects can depend on inappropriate activation of iNKT-cells (such as in psoriasis) but also on defects in their immunoregulatory functions (such as MS, RA).

7.10. Regulatory T-cells and Autoimmunity

There are two main types of regulatory T cells. Naturally occurring nT_{reg} are centrally-produced in thymus from naïve T-cells (T_n) by exposure to IL-2, TGF-β and Ag and include $CD4^+$, $CD25^+$ and $Foxp3^+$. Adaptive iT_{reg} are produced in the periphery in lymphocyte tissue via tolerogenic mechanisms by exposure of T_n to IL-2, TGF-β and Ag presented by tol-DC.

Differentiation of DCs to tol-DCs upon exposure to IL-10 and TGF-β (or corticosteroids) starts by expression of tolerogenic immunoglobulin-like transcripts (ILT3 and ILT4) at the same time when costimulatory molecules (CD40, CD80, CD86 and IL-12) and MHC II are down-regulated. Tol-DCs produce IL-10

and TGF-β upon Ag presentation in mucosal surfaces and induce T_h0 cells to iT_{reg} which cause oral tolerance. Production of indoleamine 2,3-dioxygenase (IDO) by tol-DC contributes to immunotolerance. H_3R/H_4R-agonist enhance cross-presentation and tolerance by deletion of autoreactive $CD8^+$ cells, whereas the presence of danger signals, such as TLR-ligands and GM-CSF, would favor formation of $CD8^+$ effector T cells.

In humans, Foxp3 is not restricted to iT_{reg}, which can be recognized as $CD127^{lo}$, $CD25^+$ and $CD4^+$ cells. IL-10-produces inducible type 1 regulatory T cells (Tr1 T_{reg} and TGF-β- Th3 T_{reg}, which both are $Foxp3^-$. Regulatory T cells in general down-regulate immune activation by producing IL-10, TGF-β and IL-35 (Burrell et al. 2012), by expressing immunosuppressive surface molecules, such as CTLA-4, and by inducing production of IDO in APC. H_4R-agonists are chemotactic to T_{reg} and can stimulate IL-10 production (Morgan et al. 2007).

Regulatory B10 cells are produced when B10-cell precursor via BCR is stimulated by an auto-Ag. Auto-Ag is internalized and its determinants are presented in a B-cell surface MHC II to TCR, whereas a B-cell surface CD40 stimulates the T-cell via CD154. This induces T-cell produces interleukin-21, which via B-cell surface IL-21R stimulates the matured B10 cell to produce IL-10 to down-regulate T-cell function.

7.11. Atopic Dermatitis and Inflammatory Skin Diseases

The natural history of atopic manifestations ("allergic march") is characterized by a sequence of atopic dermatitis and food allergy (peak prevalence at the age of 1 year), followed by asthma (peak prevalence at the age of 5-8 years) and finally allergic rhinitis (and conjunctivitis) reaching a peak plateau at the age of 12 years. Increased lesional histamine concentrations have been described in prick-tests, urticaria, allergic contact dermatitis and psoriasis (Thurmond et al. 2008; Gutzmer et al. 2011), but in spite of some older suggestive studies, the situation is not clear in atopic dermatitis (Ständer & Steinhoff 2002). In a dog model for atopic dermatitis, histamine increased only locally for 1-3 hours after challenge (Bäumer et al. 2011). H_1R-antagonists have incomplete effects and it has therefore been suggested that maybe H_4R modulation could be helpful here. H_4R has been shown in keratinocytes, dermal fibroblasts, MCs, eosinophils, dermal DCs, LCs and nerve cells in the skin, but this depends on the differentiation, localization and external stimuli (Damaj et al. 2007; Dijkstra et al. 2008; Ikawa et al. 2008; Gschwandtner et al. 2010). H_4R is higher in the upper than in the lower epidermis (Yamaura et al. 2009) and stimulation with LPS, indomethacin and dexamethasone increases H_4R mRNA and/or protein in dermal fibroblasts.

Atopic dermatitis is characterized by increased numbers of MCs in skin lesions and often dietary or pollen allergies. Increased serum IgE values (Liu et al. 2011)

correlate positively with the disease activity and treatment with anti-IgE (e.g. omalizumab) is occasionally effective. IDEC are characteristic for atopic eczema and disappear upon successful treatment (Wollenberg et al. 1996; Wollenberg et al. 2001). Acute atopic dermatitis is characterized by a Th2 response (IL-4, IL-5, IL-13) but a chronic disease by Th1 milieu (IFN-γ) and lichenification, epidermal hyperplasia and dermal fibrosis caused by scratching (Dijkstra et al. 2008; Simon et al. 2004). Dermal eosinophil infiltrates are prominent and eosinophilic cationic protein ECP can be used to evaluate disease activity.

Three different single nucleotide polymorphisms (snp) have been described in HRH4 gene coding H_4R in atopic dermatitis, suggesting that this receptor may play a role (Yu et al. 2010). MC and eosinophil H_4R may mediate chemotaxis. IDEC is H_4R positive and stimulation of H_4R (but not modulation of the other histamine receptors) of IDEC led to diminished production of Th2-chemokine CCL2 (attracting monocytes, activated T-cells and NK-cells) and Th1-polarizing cytokine IL-12 (Dijkstra et al. 2008), suggesting that low level histamine, if maintained, may down-regulate the immune-inflammatory activity of these cells.

LCs in atopic dermatitis can probably act as pro-inflammatory, immunosuppressive or tolerogenic cells. LCs express functional H_4R which by low histamine concentrations or by specific H_4R-agonists down-regulates CCL2 production. This also increases their migration *ex vivo* from the skin, normally indicating migration towards secondary lymphatic organs (Gschwandtner et al. 2010; Chu et al. 2011).

Th1, Th2 and Th17 cells are immunological effector cells in human inflammatory skin diseases and they can all express H_4R (Mommert et al. 2011), which is *in vitro* upregulated by the Th2 cytokine IL-4. H_4R stimulation increases production of pruritogenic IL-31 (Gutzmer et al. 2009), in particular in atopic dermatitis.

Also chronic idiopathic urticaria is associated with increased MC numbers, in which disease IgG auto-Ab against the FcεRI can trigger MC degranulation. MCs in skin express mostly H_2R and H_4R (Lippert et al. 2004). In a FITC-induced Th2-driven inflammatory contact dermatitis in mice H_4R-antagonists had anti-inflammatory effects (Cowden et al. 2010b), perhaps via DC by diminishing their mobilization from skin to lymph nodes and thus Th2 polarization. Symptomatic effects were not seen in MC-KO mice suggesting that here H_4R-antagonists acted directly on MCs. Similar results, combined with diminished serum IgE levels, were obtained in a TNCB-driven mouse model with H_4R antagonists started before sensitization and continued during TNCB-treatment (Suwa et al. 2011). In contrast, in an acute dog (Bäumer et al. 2011) and mouse (Seike et al. 2010) models H_4R-antagonists were not helpful.

Recently, dual inhibition of H_1R/H_4R has been advocated (Matsushita et al. 2012; Ohsawa et al. 2012). Monotherapy with H_4R-antagonist diminished IL-4, IL-5 and IL-6, but increased IL-12 and IFN-γ. Increase of IL-12 and IFN-γ

was not seen in animals treated with dual inhibition. Dual inhibition helped against itch and was as effective in the overall treatment as prednisolone for which it might offer an alternative in the future. In contrast to H_1R-antagonist, H_4R-antagonist had an effect both on histamine and substance P induced itch (Yamaura et al. 2009), which may be mediated directly via H_4R^+ sensory nerves (Dunford et al. 2007), where H_3R inverse agonist caused dose-related itch which was totally blocked by a combined treatment with H_1R- and H_4R-antagonists (Rossbach et al. 2011). Therefore, it was concluded H_1R and H_4R stimulation and H_3R-inverse agonist all cause itch (and calcium increase in the neuronal cells).

7.12. Asthma

Asthma is a chronic, inflammatory and often immune-based disease that mostly targets the small contractile bronchioles of the airways, characterized by a smooth muscle wall and eosinophil, MC and T-cell infiltrates (Bousquet et al. 2000). Dyspnea, cough and wheezing are typical symptoms. These features are inducible by H_1R-agonists, but in spite of this H_1R-antagonists are not effective in the treatment of asthma (Thurmond et al. 2008). Asthma may be extrinsic (atopic, with type 1 hypersensitivity to allergens) and intrinsic (non-atopic) and both Th2 lymphocytes/IgE/MC and innate helper type 2(I_h2)/IL-5/eosinophils play important roles in it.

Chemokines and cytokines are not only produced by the rapidly acting MCs, basophils and eosinophils, but also by DC, macrophages and in particular T- and B-cells, which are readily present in newly-diagnosed asthma (Laitinen et al. 1993). In untreated and newly diagnosed airway epithelium (BALF may not accurately reflect tissue events), 612 lymphocytes (110 in controls, $p<0.05$), 120 MCs (7 in controls, $p<0.001$), 75 eosinophils (0 in controls, $p<0.05$), and 15 macrophages (0 in controls, $p < 0.05$) per mm^2 were counted (Laitinen et al. 1993). The situation was possibly further lymphocyte-dominated in airway lamina propria, where the lymphocyte values were 656 *vs.* 155 ($p<0.001$), plasma cells were 285 *vs.* 27 ($p<0.001$), macrophages were 44 *vs.* 3 ($p<0.001$) and monocytes were 11 *vs* 1 (NS), whereas the MCs were 124 *vs.* 88 (NS) and eosinophils were 134 *vs.* 3 ($p<0.001$). These findings suggest that asthma may basically be a lymphocyte-based immunological disease.

As demonstrated by the cellular pathology above, asthma and other atopic diseases can be divided to two different phases, the sensitization phase and the challenge phase (Little et al. 2003). In the sensitization phase, the mucosal membrane and mucosal-associated lymphatic tissue (MALT)) are exposed to a potential aeroallergen (Bielory et al. 2013), leading to IgE production in type 2 response in pulmonary hilar lymph nodes with involvement of DCs, $CD4^+$ T-cells, $CD8^+$ T-cells, B-cells and plasma cells.

Type 2 macrophage polarization is characterized by suppression of pro-inflammatory cytokines, intracellular killing and Ag presentation, but accompanied by production of moderate levels of IL-10 (Gordon et al. 2003; Martinez et al. 2009). Membrane receptors with scavenger function are upregulated together with a variety of molecules implicated in tissue regeneration, wound healing, granuloma formation and immunity against large parasites (Martinez et al. 2009). Via inducation of arginase 1, arginine metabolism shifts from production of NO to production of L-ornithine, utilized to produce polyamines and proline important for cell growth and collagen synthesis. M2 macrophages secrete chemokines such as CCL17, CCL18, CCL22 and CCL24 which recruit Th2 cells, basophils and eosinophils (Mantovani et al. 2004). IgE antibodies produced do not fix complement and do not pass placenta and form only 0.05% of serum immunoglobulins. However, they are empowered by binding to high affinity FcεRI IgE-receptors on the surface of highly explosive MC and basophils.

H_4R has been shown in most leukocytes, which are believed to play a role in asthma (Gantner et al. 2002). Stimulation of H_4R causes MC and eosinophil chemotaxis (Hofstra et al. 2003) and increases CD11b/CD18 and ICAM-1 adhesion molecules on eosinophils (Buckland et al. 2003; Ling et al. 2004; Barnard et al. 2008). H_4R mRNA has also been shown in non-immune cultured cells originating from lung tissue, including smooth muscle cells, epithelial cells and vascular endothelial cells. Experimental data suggest that H_4R-antagonist JNJ 7777120 administered perorally diminishes T cell infiltration into lung tissue in already established airway inflammation (Cowden et al. 2010a).

Upon Ag challenge, IL-16 increases in BALF in both patients and experimental asthma models. Histamine stimulates production of IL-16 in pulmonary epithelial cells and $CD8^+$ T-cells (Cruikshank et al. 2000; Gantner et al. 2002). The stimulating effect of histamine on $CD8^+$ T-cells is mediated via H_2R and H_4R, but in asthma most IL-16 is probably derived from epithelial cells. The amount of IL-16 in BALF correlates with the $CD4^+$ T-cell infiltrates in asthma (Cruikshank et al. 2000). This agrees with the observation that IL-16 binds to the CD4-receptor and promotes recruitment of $CD4^+$ cells. In OVA-sensitized mice, intra-tracheal administration of IL-16 before OVA challenge lead to inflammatory inilftrates and diminished Th2-cytokine IL-5 in BALF (Little et al. 2003). This could be due to recruitment and induction of T_{reg} (McFadden et al. 2007).

DCs have a capacity to act in a tolerogenic, anti-inflammatory or pro-inflammatory way, but the factors regulating the type of DC response are not known in detail. Histamine *in vitro* can stimulate migration of monocyte-derived cDC via H_2R and H_4R (Gutzmer et al. 2005). The same study reported that stimulation of cDC via H_4R inhibited production of Th1-cytokine IL-12 and therefore promotes Th2-cytokine milieu. Screening of gene expression in histamine stimulated cDC demonstrated increased expression of certain Th2-related cytokines, such as TNF-α and TGF-β2 (Lundberg et al. 2011).

However, histamine stimulation also causes gene expression of various chemokines and cytokines that are related to Th1-, Th17- and T_{reg}-mediated immune responses. Histamine affected the maturation of DCs via H_1R and H_4R. The neutral H_4R-antagonist JNJ7777120 inhibited allergen-provoked T-cells *in vitro*.

Conflicting results have also been published. Inhalation of 4-MeHA, which is a double agonist of H_4R and H_2R (with approximately 100-fold preference for H_4R) inhibited OVA-induced inflammation, probably due to the T_{reg} recruitment to lungs (Morgan et al. 2007) or indirectly via effects on DCs. It is possible that this difference is simply caused by a different route of drug application, as inhaled 4-MeHA causes a local chemotactic concentration gradient to H_4R and H_2R positive leukocytes, whereas a systemic or genetic inhibition of H_4R and H_4R antagonists directly inhibit H_4R^+ cells everywhere (Cowden et al. 2010a; Dunford et al., 2006).

7.13. Allergic Rhinitis

Allergic rhinitis, either seasonal or persistent/perennial, is characterized by recurrent sneezing, increased mucus production, obstruction of the nasal passages and itching. (Skoner et al. 2001). It has a strong genetic component favouring development of Th2-IgE-MC-mediated immune responses upon challenge and sensitization to allergens. Common allergens are fecal proteins from dust mites, cat and dog dandruff and pollen. The central mechanism in the sensitization phase is DC-mediated Ag presentation to T_h0 cells favoring polarization to IL-3, IL-4, IL-5 and IL-13 producing Th2 cells and plasma cell-mediated production of IgE antibodies. Upon Ag re-challenge nasal mucosal membranes become infiltrated by MC, eosinophils and plasma cells. Also basophils have been found in nasal lavage fluid in such patients (Shiraishi et al. 2013). Local or systemic administration of H_1R-antagonists, local sympathomimetic drugs (pseudoephedrin) and local corticosteroids are used in its treatment.

H_1R is expressed on the epithelial, endothelial and neural cells in the lower nasal passages, H_2R on epithelial and glandular (mucus production) cells and both H_3R and H_4R on neural cells (Nakaya et al. 2004). It has been proposed that H_3R participates in the homeostatic maintenance of the nasal mucosa and regulates mucus production (Suzuki et al. 2008). Phase II clinical study did not find any advantage of H_1R/H_3R antagonist over H1R antagonist upon exposure to allergen in a challenge chamber (Daley-Yates et al. 2012).

Experimental animal studies showed that repeated local administration of H_4R-antagonist JNJ7777120 decreased sneezing and scratching of the nose at only 1 nM concentration (Takahashi et al. 2009). Repeated peroral administration

decreased serum IgE concentrations while decreased IL-4and increased IFN-γ levels were found concurrently in nasal lavage fluid, which is notable because IL-4 and IFN-γ increase and decrease plasma cell-mediated IgE production. Results encourage to further studies of single or double action drugs.

H_4R-antagonists could possibly have symphatomimetic, pseudoefedrin-like effects via induced endogenous cathecolamine release (Chan et al. 2012). Inhibition of H_4R with antagonists or gene knockout is antipruritogenic and stimulation of H_4R with histamine causes itch, with a similar effect obtained via manipulation of H_1R (Dunford et al. 2007; Thurmond et al. 2008; Rossbach et al. 2011). A third possible mechanism of action could relate to diminished MC and eosinophil chemotaxis along with diminished DC, Th2 and plasma cell dependent IgE synthesis, which would affect both the acute and chronic phase of allergic rhinitis.

7.14. Allergic Conjunctivitis

Allergic conjunctivitis is characterized by bilateral itch, burning, redness, tearing and swelling of the conjunctiva and lids. Seasonal allergic conjunctivitis (SAC) and perennial (persistent) forms (PAC) are relatively mild Ag-driven diseases, but atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC) can affect the cornea and vision (Bonini et al. 2009). Comorbidity between AKC, allergic rhinitis, atopic dermatitis, urticaria and asthma is common, suggesting shared disease mechanisms in form of sensitization and subsequent challenge phases. Although specific allergens cannot be shown in a large proportion of VKC-patients, inflammation is Th2-driven with increased histamine concentrations in tear fluid (Leonardi et al. 2011), which may contribute to pathological tissue remodeling and chronicity. As a result, local and peroral H_1R-antagonists, mast cell-stabilizing drugs (such as cromoglycate and nedochromil) and corticosteroid eye drops form the mainstay of treatment (Bonini et al. 2009). In difficult cases, immunosuppressive calcineurin-inhibitors and sometimes desensitization can improve tolerance to allergens.

Locally administered levocabastine (H_1R-antagonist) and JNJ7777120 (H_4R-antagonist) diminished scraping response, hyperemia and swelling in a dose-dependent manner in a 2-10 μM histamine-induced experimental mouse model, but statistical significance was only seen for the H_1R-antagonist, but the most potent effect was obtained by combined use (Nakano et al. 2009). Immunostaining revealed increased H_1R, H_2R and H_4R levels in conjunctival cells for VKC patients compared to controls (Leonardi et al. 2011), which was confirmed by messenger RNA levels that were 5-fold increased for H_2R and H_4R. H_1R was particularly increased on vascular endothelial cells and H_4R in stromal inflammatory cells. Expectations of H_4R-modulators are high but require conformation by randomized clinical trials.

7.15. Rheumatoid Arthritis

Reumatoid arthritis (RA) is a symmetrical autoimmune polyarthritis of usually small, peripheral synovial joints associated with rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA). Its midline symmetry and involvement of the most densely innervated small peripheral joints (with widest representation in hominiculus) has evaded firm explanations, but the most strongly advocated theory refers to neurogenic inflammation (Konttinen et al. 1994). This is interesting considering the close spatial and functional relationship between small peripheral C and Aδ neuropeptide nerves and MC (Hukkanen et al. 1991) combined with the presence and role of H_3R and H_4R in the function of those nerves. Furthermore, MCs produce corticotropin-releasing hormone (Kempuraj et al. 2004) and respond to it (Cao et al. 2006), suggesting the hypothalamus-pituitary-adrenal or HPA axis might participate in the pathogenesis of RA similar to the arthritis model in Lewis rats (Sternberg et al. 1989).

The fundamental cause of RA is unknown and it has been suggested that the triggering stimulus (loss of tolerance) and the perpetuating stimulus (chronicity) are different, such as an initial triggering infection causing a mostly continuous release of cartilage-derived damage-associated molecular patterns (DAMPs) and auto-Ag. In this context, it is interesting to note that in rheumatoid synovitis, mature DCs capable of presenting antigen and activated cytokine-producing T-cells do not recur to the joint from which all cartilage has been removed in association to total joint replacement (Li et al. 2001; Li et al. 2002).

Synovitis is the best known pathological manifestation of RA, although its pathology is also evident in the bone marrow and it can be assumed that the preclinical immunological processes occur in the lymphoid organs. Synovitial stroma is characterized by the presence of MHC II^+ macrophages, specifically $CD4^+$ T-cells and plasma cells, but also by DCs, MCs, fibroblasts, endothelial cells, adipocytes and peripheral nerve fibers and terminals. Synovial lining is composed of fibroblast-like type B lining cells and macrophage-like type A lining cells. Cultured RA (fibroblast-like synoviocytes) contain mRNA coding H_1R, H_2R and H_3R but lack H_4R coding mRNA (Ikawa et al. 2005) but the presence of the H_4R protein was detected by double staining in proline-4-hydroxylase-positive synovial fibroblasts and in $CD163^+$ macrophages (Ohki et al. 2007).

Current disease intervention is based on commencement of early treatment with evidence-based, methotrexate-achored combinations with disease-modifying anti-rheumatic drugs (DMARDs), modified according to patient response (saw tooth principle) and guided by fixed goals using the treat-to-target (T2T) principles, in modern times strongly supported by biological anti-rheumatic drugs (biologicals). Biologicals are highly selective drugs with targeting entities such as TNF (infliximab, etanercept, adalimumab, certolizumab pegol, golimumab), IL-1 (anakinra), IL-6Rα (tocilizumab), CD80/CD86 co-

stimulatory molecules (abatacept) or CD20/B-cells (rituximab). Janus kinase 3 tyrosine kinase inhibitor tofacitinib is the latest newcomer.

Synovitis is characterized by increased numbers of MC, which are also located at the site of cartilage destruction in the pannus tissue. However, early studies using adjunctive treatment with antihistamines (H_1R-antagonists) (Wilson 1953) and H_2R antagonists (Permin et al. 1981) failed, resulting in the relegation of histamine to an epiphenomenon rather than active molecular participant.

It was therefore notable that inhibition of c-kit tyrosine kinase, typically present in MCs, diminished disease activity including the number of tender and swollen joints, ESR and CRP (Eklund & Joensuu 2003). C-kit is a tyrosine kinase receptor (mast/stem cell growth factor receptor) for stem cell factor (SCF), previously annotated as Steel factor or kit-ligand.

In spite of early observations suggesting increased plasma and in particular synovial fluid histamine levels, implying intra-articular release (Frewin et al. 1986), a more recent finding suggests decreased plasma levels and significantly decreased synovial fluid levels of histamine (Adlesic et al. 2007). RA serum histamine was 0.93± 0.16 ng/mL compared to 1.89 ± 0.45 ng/mL in controls ($p<0.001$) and the RA synovial fluid histamine levels were only 0.37 ± 0.16 ng/mL ($p<0006$). Histamine levels increased in aTNF-treated RA patients ($p<0.01$). These authors also injected 20 µL fluid containing 10, 1, 0.1 or 0.01 ng histamine intra-articularly into healthy joints or joints challenged with a preceding intra-articular injection of high mobility group box-1 (HMGB1, an endogenous DAMP) or peptidoglycan (a pathogen/microbial-asssociated danger signal, PAMP/MAMP). Histamine produced no effects by itself or in induced arthritis. This led the authors to propose that histamine lacks harmful properties in RA (Adlesic et al. 2007).

What is clear from the above experiments is that histamine levels in RA are at nanomolar levels (0.11 ng/mL histamine corresponds to 1 nM) and $10^{-8.1}$ M histamine is sufficient to half-maximally activate H_4R. MC activation may locally and temporarily increase histamine levels to micromolar concentration range, but due to histamine degradation, uptake, binding and diffusion this increase is transient. In contrast, how the low but constitutitively present nanomolar histamine levels rather than micromolar levels affect processes such as DC_0 and T_h0 cell polarization and Ag presentation in RA remain open at present. In RA tissues, $CD304^+$ (BDCA4) pDCs producing IL-18 and IFN-α/β are more common than $CD1c^+$ (BDCA1) cDCs expressing IL12 and IL-23 and their numbers correlate with RF and ACPA (Lebre et al. 2008). Indeed, pDCs express H_4R. H_4R-agonists diminished pDC mediated TFN-α, IFN-γ and CXCL8 production. H_2R had similar effects, but it is not known whether the histamine levels in RA joints reach H_2R-stimulatory concentrations (Gschwandtner et al. 2011).

7.16. SLE

Systemic lupus erythematosus (SLE) is a systemic autoimmune and immune complex disease in which clearance of immune complexes and apoptotic cell rests seems to be impaired with nuclear auto-Ags being especially targeted. American College of Rheumatology classification criteria define 12 different symptoms and signs where if at least four of these symptoms are positive, the condition can be classified as SLE (Hochberg 1997).

HRH4 gene transcripts (H_4R coding mRNA) were high in SLE compared to healthy controls. Interestingly, amplification in HRH4 copy numbers (>2 HRH4 copies) was associated with increased incidence of anti-nuclear antibodies, arthritis and proteinuria, whereas copy number deletions (<2 HRH4 gene copies) were found to be protective against proteinuria (Yu et al. 2010). This seems to demonstrate the influence of gene copy-number variation (CNV) on the disease phenotype. In SLE, an increased HRH4 gene copy number seems to lead to higher H_4R mRNA copy numbers, which can cause disturbances in the nanomolar histamine-H_4R interactions which subsequently affect the disease severity.

7.17. Sjögren's Syndrome

Sjögren's syndrome (SS) is a female dominant (90%) autoimmune disease of the exocrine glands, which can occur in primary form but also as a secondary form in disorders such as RA and SLE. It is characterized by keratoconjunctivitis sicca and xerostomia in association with focal sialadenitis and SS-autoantibodies (Shiboski et al. 2012).

It is well known that local sialadenitis and local numbers of MC correlate to each other in SS salivary glands (Konttinen et al. 1990). At that time, histamine was expected to perhaps play a role via H_1R and/or H_2R, although it had earlier been shown that intra-arterial injection of 100 nM histamine causes an early, short-term (~60 s) increase in blood flow and salivation, followed by a later, longer lasting (15-20 minutes) response, which was partially inhibited by H_1R-antagonist but not affected by H_2R-antagonist and was found to be neutrally-mediated without any direct effect on acinar cells (Shimizu & Taira 1980).

More recently, H_4R were found on some infiltrating leukocytes as well as acinar and ductal epithelial cells in healthy human salivary glands. In contrast, H_4R expression on these glandular cells was highly decreased in SS (Stegaev et al. 2012), suggesting that this epithelial H_4R downregulation is due to repeated exposure to micromolar, burst release histamine in diseased SS salivary glands. This may also explain the relatively weak H_4R expression in the infiltrating lymphocytes. Epithelial H_4R was shown at the mRNA, receptor protein and functional level and it seems that these cells are non-professional histamine producing cells containing 74-kDa HDC, which may participate in the modulation of the off-state nanomolar

histamine concentrations apparently necessary for the tissue homeostasis. Furthermore, acinar and ductal epithelial cells contained OCT3, which seems to allow histamine uptake for intracellular degradation at 100 nM concentrations but also allows intracellular histamine release during off-state. In SS, OCT3 levels were low, suggesting that the cells are incapable of buffering against burst-released histamine, which would partially explain the local downregulation of H_4R on resident and immigrant cells (Stegaev et al. 2013).

7.18. Ulcerative Colitis

Ulcerative colitis (UC) is an IBD considered as an autoimmune disease, in part because of several disease-activity-associated or independent extra-intestinal autoimmune manifestations and the immunosuppressive treatment used in the disease management. It affects the colon by causing superficial Th2 helper T-cell-dominated mucosal infiltrates, inflammatory cryptitis and ulcerative lesions. Th17 helper T-cells might also participate. Upon increasing severity, the number of blood and mucus mixed stools per day increases, malaise, fatige and fever appear as general symptoms, the inflammatory parameters CRP and ESR increase and blood hemoglobin decreases, possibly resulting in toxic megacolon and rupture. Although basically affecting the colon, some back-wash ileatitis often also occurs.

In a steroid-resistent UC, a combination of H_1R-antagonists, MC stabilizers and a hypoallergenic diet have been preliminarily found to be useful and suggest a role for burst release histamine in severe disease and disease exacerbation (Raithel et al. 2007). ECL cell and MC-derived histamine is supposed to play an important role in the initial increase of the vascular permeability characteristic for UC (Coron et al. 2012). Urinary secretion of the HNMT-produced histamine degradation product N-methylhistamine is increased in UC and Crohn's disease and correlates with disease activity (Winterkamp et al. 2002). Polymorphic, mutated DAO is associated with the severity of UC (García-Martin et al. 2006). Disturbances in nerve-derived and bacterially-produced histamine may further disturb the local histamine milieu and interfere with DC-T-cell co-operation but also with angiogenesis and fibrosis. H_4R antagonists diminished macroscopic damage, myeloperoxidase, TNF-α, wall thickness and neutrophil infiltratation when administered 24 hours before induction of an acute colitis model in rats using exposure to trinitrobenzene sulphonic acid (Varga et al. 2005).

7.19. Crohn's Disease

Crohn's disease was earlier called terminal ileitis due to the common involvement of this segment of the intestine. However, this disease can affect any part of the human gastro-intestinal tract, often as skip lesions with intact and apparently

uninvolved bowel segments in between the focal and segmental leasions. Crohn's disease is characterized by abdominal pain, weight loss, fever, diarrhea, transmural involvement of the bowel wall (with peri-intestinal abscesses, fistuli and bowel stenosis. and extra-intestinal symptoms as well as anti-inflammatory and immunosuppressive medication. Its histology is characterized by intraepithelial neutrophils, cryptitis, Th1/Th17 response and non-caseating granulomas. Although H_4R is supposed to play a role in the regulation of the polarization of T_h0 cells, there is at present little knowledge on this aspect in Crohn's disease. Interactions between PAMP/MAMP and bacterial Ags with DCs and their subsequent interactions with T_h0 T-helper cells have been proposed to regulate the balance between T_{reg} and T_{eff} in a context-dependent manner in IBD (Himmel et al. 2008).

The H_1R-agonist HTMT-dimaleat, H_2R-agonist dimaprit, H_3R-agonist (R)-(-)-α-methylhistamine and H_4R-agonist 4-methylhistamine can excite enteric neurons in human submucosal plexus, where the receptor specificity of this excitation was proven by demonstrating blockage with a corresponding antagonist. Considering the role of the autonomic enteric nerves of the intestine as regulators of the bowel function, this implies a novel and interesting aspect for IBD (Breunig et al. 2007) and emphasizes the role of the neuro-immuno-endocrine aspects of autoimmune diseases (Lomax et al. 2005; Wood 2004).

In addition to nerves, H_1R, H_2R and some H_4R have been described in enterocytes, H_1R and H_2R in muscle layer and H_1R, H_2R and some H_4R in immune cells (Sander et al. 2006).

7.20.Glomerulonephritis

One rare form of rapidly progressive glomerulonephritis is the anti-glomerular basement membrane-induced Goodpasture's syndrome. An experimental model of Goodpasture's syndrome can be treated with histamine, which decreased proteinuria, macrophage infiltration and crescent formation. It also decreased concentrations of IL-12, a well-known Th1 polarizing cytokine. These effects were specifically inhibited by an H_4R-antagonist but not affected by H_1R- and H_2R-antagonists (Tanda et al. 2007), although an earlier study published when only H_1R and H_2R were known used only H_1R- and H_2R-antagonists and argued that histamine plays no role in Goodpasture's syndrome (Wilson et al. 1981). This once more reveals how earlier work needs to re-evaluated in light of new findings. There are currently no observations on H_4R status and function in the more common forms of glomerulonephritides.

7.21. Autoimmune Diseases of the CNS

Several lines of evidence suggest a key regulatory role of histamine in the widely used experimental autoimmune encephalomyelitis (EAE) murine model,

with CNS myelin proteins as potential auto-Ags (Musio et al. 2006; Lu et al. 2010; Passani & Ballerini 2012). Therefore, the regulatory functions of histamine relevant to the onset and progression of neuroinflammatory diseases and EAE in particular are being studied in genetically modified mice lacking histamine receptors and with selective agonists and antagonists. It is becoming evident that histamine plays a complex role with variable and occasionally contradictory effects, depending on the receptor subtypes being activated and the specific targeted tissue (Table 7.2).

All histamine receptors are expressed on cells involved in autoimmune diseases, with the exception of the H_3R that is normally not expressed by hematopoietic cells and is mostly confined to the CNS (Passani & Blandina 2011). Susceptibility to EAE requires expression of Hrh1, the gene encoding H_1R in mice (Ma et al. 2002). H_1R is expressed on Th1 cells in EAE mice brain lesions (Pedotti et al. 2003) where its presence is necessary for full encephalitogenic expression (Noubade et al. 2007). Furthermore, expression of H_1R is upregulated on encephalitogenic PLP139-151-specific Th1 compared to Th2 cell lines. Unsurprisingly, specific pharmacological antagonists targeting H_1R result in amelioration of EAE (Pedotti et al. 2003; El Behi et al. 2007) and H_1R-knockout mice exhibit a significant delay in the onset of EAE and a reduction in the severity of clinical signs compared with WT mice. Indeed, $CD4^+$ T-cells from H_1R-knockout mice produce significantly less IFN-γ and more IL-4 (which induces differentiation of naïve $CD4^+$ T cells to Th2 cells) in *in vitro* assays compared to wild-type controls, indicating that H_1R signaling in $CD4^+$ T cells plays a central role in regulating pathogenic T-cell responses (Ma et al. 2002).

H_2R also seems to partially regulate encephalitogenic Th1-cell responses and EAE susceptibility, as H_2R-knockout mice develop a less severe disease than wild-type littermates during the acute, early phase (Teuscher et al. 2004). The failure of H_2R-knockout mice to generate encephalitogenic Th1 effector cell responses is attributed to H_2R-mediated regulation of cytokine production by DCs, which affects T-cell-polarizing activity. In conclusion, H_1R and H_2R seem to have pro-inflammatory and disease-promoting effects, but H_1R or H_2R activation may also play an important role in limiting autoimmune responses, meaning their biological action is probably more complex. This complexity is further suggested in an EAE mouse model, where H_1R and H_4R produced pro-inflammatory effects but H_2R and H_3R produced anti-inflammatory effects on the disease process (Jadidi-Niaragh & Mirshafiey 2010).

As mentioned above, H_3R are normally not expressed by hematopoietic cells and are mostly confined to the CNS where they limit histamine synthesis and release (Passani & Blandina 2011), and regulate release of other neurotransmitters (Blandina et al. 2010). Deletion of the H_3R gene leads to more severe EAE, an effect associated with altered BBB permeability and increased expression of chemokines/chemokine receptors that promote the entry of peripheral T cells

Table 7.2
Histamine receptors and EAE. APC, antigen presenting cells; BBB, blood brain barrier; mDC, myeloid dendritic cells; MOG_{35-55}, Myelin Oligodendrocyte Glycoprotein; $PLP_{139-151}$, Myelin Proteolipid Protein.

Histamine receptor	EAE	Investigated Cell Types	Pharmacological target	Disease outcome	Reference
H_1	SJL mice $PLP_{139-151}$	Increased H_1R expression on Th1 cells Humoral immune responses	H_1R antagonism	Less severe disease	Pedotti et al., 2003 El Behi et al., 2007
	MOG_{35-55} H_1R-KO mice	$CD4^+$ T cells		Reduced IFN-g, increased IL-4 Less severe disease	Ma et al., 2002 Noubade et al., 2007
	MOG_{35-55} H_1R-KO mice	Endothelial cells	H_1R overexpression	Restored BBB integrity Less severe disease	Lu et al., 2010
	$PLP_{139-151}$ SJL mice	$CD3^+$ T cells	H_1R activation	Reduced IFN-g Decreased endothelial adhesiveness	Lapilla et al., 2011
H_2	MOG_{35-55} H_2R-KO mice	APC Th1		Reduced cytokines Inhibition of cell polarization Less severe disease	Teuscher et al., 2004
	MOG_{35-55} C57/Bl6	Proinflammatory cells	H_2R activation	Less severe disease	Emerson et al., 2002
	$PLP_{139-151}$ SJL mice	$CD3^+$ T cells	H_2R activation	Reduced IFN-g Decreases endothelial adhesiveness	Lapilla et al., 2011
H_3	MOG_{35-55} H_3R-KO mice	Th1 Endothelial cells		Increased expression of chemokines/chemokine receptors BBB deregulation More severe disease	Teuscher et al., 2007
H_4	MOG_{35-55} H_4R-KO mice	Treg Th17		Lower frequency Higher frequency More severe disease	del Rio et al., 2012
	MOG_{35-55} C57/Bl6 mice	Th1 mDC	H_4R antagonism	Increased IFN-g, reduced IL-10 More severe disease	Passani et al., 2011

Modified from Passani and Ballerini (2012)

not expressing H_3R into the CNS (Teuscher et al. 2007). The authors suggest that neuronal H_3R may serve as a central control of cerebrovascular tone and decreases susceptibility to neuroinflammatory diseases. These results indicate that activation of H_3R may have beneficial effects.

Recent evidence has mapped the topological and functional localisation of H_4R in the CNS of humans and rodents, respectively (Strakhova et al. 2009; Connelly et al. 2009).

H_4R is detected on hematopoietic progenitor cells that enter the cell cycle upon stimulation (Petit-Bertron et al. 2009). Activation of H_4R by agonists before exposure to growth factors leads to a profound decrease in the percentage of cycling cells (Schneider et al. 2011). The H_4R expression is dynamic, as it is upregulated during the differentiation of human monocytes to dendritic cells (Gutzmer et al. 2005). In addition, receptor levels change with the progression of pathophysiological responses, such as the upregulation of H_4R expression in monocytes in response to inflammatory stimuli (Dijkstra et al. 2007), in kidney putative tubule cells in diabetic rats (Chazot, Rosa et al., manuscript submitted) and in putative immune cells at the early stage of inflammatory pain states (Chazot et al., unpublished). Furthermore, pilot data revealed that H_4Rs are expressed on the soma of both Aδ and C-fibre sensory neurons through intense staining of small and medium diameter neurons as well as lamina I-III of the rat lumbar spinal cord, where the immunoreactivity pattern suggests localisation with terminals of primary afferent neurons (Katebe M et al. 2012; Lethbridge & Chazot 2010).

Surprisingly, H_4R-knockout mice develop a more severe EAE together with increased neuroinflammatory signs compared to WT mice (del Rio et al., 2012). As genetically modified mice may carry alterations of systems other than the targeted ones and activation of vicarious mechanisms may hinder the effects related to the deleted gene, we recently studied myelin oligodendrocyte glycoprotein $(MOG)_{35–55}$-induced EAE in C57BL/6 mice treated with JNJ-7777120 (Ballerini et al., submitted to Br J Pharmacol). JNJ-7777120 was injected i.p. daily starting at day 10 post-immunisation. Disease severity was monitored by clinical and histopathological evaluation of inflammatory cells infiltrating into the spinal cord, anti-MOG_{35-55} antibody (Ab) production, T cell proliferation by $[^3H]$-thymidine incorporation, mononuclear cell phenotype by flow cytometry, cytokine production by ELISA assay and transcription factor quantification by mRNA expression. We found that treatment with JNJ-7777120 worsened the severity of EAE and increased inflammation and demyelination in the spinal cord of EAE mice. We also showed that during disease progression, T lymphocytes of JNJ-7777120-treated EAE mice produce more IFN-γ than vehicle-treated controls and fewer regulatory cytokines such as IL-4 and IL-10, despite unchanged frequency and proliferative capacity in response to MOG_{35-55}. Furthermore, JNJ-7777120 did not affect anti-MOG_{35-55} Ab production or mononuclear cell

phenotypes. Hence, our results are in agreement with the recent report that mice which do not express H_4R exhibit an exacerbated disease and immunopathology (del Rio et al. 2012). This was ascribed to impaired formation of T_{reg} T-cells and their impaired chemotaxis and suppressor activity, leading to an increase in the Th17 T-cells.

7.22. Future Visions

Histamine is produced slowly by 73-kD HDC and released gradually via OCT2/3 and PMAT ion channels without storage phase by non-professional histamine-producing cells at low nanomolar concentrations, which only affect the high affinity H_3R/H_4R-equipped DCs, T-cells and other leukocytes.

This basal level H_3R/H_4R effect is during the resting "off-state" probably maintained within narrow limits by the high constitutive activation state of H_3R/H_4Rs, histamine produced by non-professional cells, histamine released by professional cells, histamine produced by intestinal microflora on one hand, and by the DAO-mediated extracellular and HNMT-mediated intracellular degradation as well as VMAT-mediated re-uptake and storage.

As this "off-state" appears to be prevailing in healthy individual during most of the time, it can be assumed that it participates in DC-T-cell interactions by favouring maintenance of tolerance, i.e. contributing to the active tolerogenic immune responses against self-Ag, which leads to production of iT_{reg} cells.

If a foreign Ag and an adjuvant (danger signal) are introduced to the system, in the context of danger a immunogenic response is produced, which leads to production of T_{eff} cells and provision of T-cell help to B-cells, which initiates T-cell-dependent, B-cell-mediated immune responses and production of antibodies. If directed against a transient foreign pathogen or vaccine, this provides immunity. If however this immune activation occurs against continuously present self-Ag, an autoimmune disease ensues.

Immediate type I immune responses cause a lot of morbidity in form of allergic responses and diseases. These diseases are mediated by professional histamine-producing cells, such as MCs and basophils. However, type I immune responses are only possible after the sensitization phase, which required cell-mediated, delayed type immune responses and production of MC/basophil-sensitizing IgE. When the IgE-sensitized MCs and basophils degranulate and release their stored histamine, short-term and locally high micromolar histamine concentrations are attained during an "on-state". The concentrations are high enough to activate the low affinity H_1R/H_2Rs.

Non-immune activation of MCs and basophils might in healthy individuals occur as a result of local irritation, in particular in sensitive mucosal surfaces or where the skin is penetrated, leading to a local reaction helping to get rid of or to dilute the local irritant. Autoinflammatory responses evoked by danger

signals, *viz.* pathogen/microbe-associated molecular patterns and/or damage-associated molecular patterns (or alarmins), might enhance this non-immune responsiveness of tissues. If the exposure continues, these naïve responses are after sensitization enhanced by immediate type I hypersensitivity responses.

It is commonly accepted that in the treatment of these allergic diseases, if possible, elimination of the allergen by sanitary measures is an effective and logic form of intervention. In both autoimmune diseases and in allergic disease modulation of the DC-T-cell interactions seems to be a useful roadmap to new therapies. Induction of immune tolerance and a shift from IgE to IgG production seem to be tempting therapeutic targets. Due to the putative role of low nanomolar histamine and high-affinity H_3R/H_4Rs, modulation of these interactions by systemic and/or local synthetic small molecular weight H_3R- and H_4R-modulators to prevent sensitization or to induce tolerance seems to be the way to go. They good replace the currently widely used and expensive biologic drugs and biosimilars, which usually influence down-stream effector effects, for example by neutralizing pro-inflammatory cytokines, and extend the spectrum of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids to biologic anti-inflammatory drugs. Interventions targeting more proximal pathogenic events at the root of the disease, treating the cause rather than the symptoms, seem more logical. The clinical and commercial success of antihistamines and H_2R blockers encourage further research of H_3Rs and H_4Rs.

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