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Histamine: an undercover agent in multiple rare diseases?

Almudena Pino-Ángeles [a, b], Armando Reyes-Palomares [a], Esther Melgarejo [a, b], Francisca Sánchez-Jiménez [a, b, *]

[a] *Dpto. Biología Molecular y Bioquímica, Universidad de Málaga, Málaga, Spain*
[b] *U741 of 'Centro de Investigación Biomédica en Red de Enfermedades Raras' (CIBERER, ISCIII), Málaga, Spain*

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Abstract

Histamine is a biogenic amine performing pleiotropic effects in humans, involving tasks within the immune and neuroendocrine systems, neurotransmission, gastric secretion, cell life and death, and development. It is the product of the histidine decarboxylase activity, and its effects are mainly mediated through four different G-protein coupled receptors. Thus, histamine-related effects are the results of highly interconnected and tissue-specific signalling networks. Consequently, alterations in histamine-related factors could be an important part in the cause of multiple rare/orphan diseases. Bearing this hypothesis in mind, more than 25 rare diseases related to histamine physiopathology have been identified using a computationally assisted text mining approach. These newly integrated data will provide insight to elucidate the molecular causes of these rare diseases. The data can also help in devising new intervention strategies for personalized medicine for multiple rare diseases.

Keywords: histamine • histamine receptors • rare diseases • systems biology

Introduction: previous knowledge and hypothesis

The biogenic amine histamine (Hia), 2-(1H-imidazol-4-yl) ethanamine, was discovered in 1910 by the winner of the 1936 Nobel Prize for Medicine, Sir Henry H. Dale [1]. It is the product of the alpha-decarboxylation of the proteinogenic amino acid histidine by the enzyme histidine decarboxylase (HDC, EC 4.1.1.22). In gram-positive bacteria, HDC activity is pyruvoyl-dependent, whereas in gram-negative bacteria and in animals, this is a pyridoxal 5-phosphate (PLP)-dependent enzyme [2, 3].

Only a reduced set of mammalian cells, known as Hia-producing cells (HPCs), expresses the HDC gene, namely, mast cells and other immune cells, gastric enterochromaffin-like cells (ECLCs) and histaminergic neurons. Newly synthesized Hia can be either stored in specialized granules, as it occurs in mast cells and basophils, or it can be released to the medium [4]. On its own, intracellular Hia can slow the G1/S progression of the cell cycle, as recently demonstrated in transfected human embryonic cells expressing active and inactive versions of HDC [5]. It can also act as a stress factor because it is degraded by amino oxidases [6]. Extracellular Hia can be taken up by organic cation transporters [7].

The major Hia-mediated effects are elicited through different signalling mechanisms dependent on target cell types [8]. In allergic reactions, Hia acts on vascular smooth muscle cells and endothelial cells, leading to vasodilation and increased vascular permeability. In the gastrointestinal system, Hia released by ECLCs act on parietal cells to stimulate H^+, K^+ ATPases, leading to acid gastric secretion. Hia is also a neurotransmitter in the central nervous system (CNS). It plays a key role in regulating the sleep–wake cycle, appetite, learning, memory and motor system [9, 10]. Thus, alterations in Hia

*Correspondence to: Francisca SÁNCHEZ-JIMÉNEZ,
Departamento de Biología Molecular y Bioquímica,
Facultad de Ciencias, Universidad de Málaga,
29071, Málaga, Spain.
Tel./Fax: +34 952131674
E-mail: kika@uma.es

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metabolism are related to diverse human pathologies, such as anaphylaxis and other inflammatory conditions, peptic ulcer, neurological disorders and cancer progression [1].

There are four different Hia receptors, named H_1R through H_4R according to the order in which they were discovered. All four belong to class A family of G-protein coupled receptors (GPCRs). They trigger different signalling pathways that depend specifically on both the receptor and the cell type expressing it [11]. H_1R couples $G\alpha_{q/11}$ proteins, leading to phospholipase C activation, production of inositol phosphate and calcium mobilization. Although H_1R has been traditionally related to the allergic response, it is also expressed in nerve cells, vascular smooth and endothelial cells among others, and takes part in neurotransmission and cellular adhesion respectively [9, 11]. H_2R is expressed in many immune cell types, parietal cells and nerve cells. H_2R mediates its effects by coupling $G\alpha_S$ proteins, stimulating adenylate cyclase and increasing intracellular cAMP levels. Due to its broad localization, antagonists of this receptor have been used for treating gastric and neurological disorders, as well as in antitumour therapy [11, 12]. H_3R, when located in the presynaptic membrane of histaminergic cells, regulates the production of Hia in the CNS; it also regulates the release of many neurotransmitters, acting as a presynaptic heteroceptor [12, 13]. H_3R couples to $G\alpha_{i/o}$ proteins and inhibits cAMP accumulation. It has been demonstrated that several active isoforms of this receptor exist in humans, although their function remain unknown. H_4R is expressed in certain immune cells of haematopoietic origin and in the CNS. Similar to H_3R, H_4R couples to $G\alpha_{i/o}$ proteins and inhibits cAMP formation. This receptor has been recently targeted as a key component of the immune response as well as being responsible for the mobilization of immune cells. Its discovery has generated new hypotheses about the possible roles of Hia in inflammatory and neurological diseases [9, 10, 14]. Owning to the plethora of processes in which it acts as a key element, Hia could be considered the most versatile biogenic amine, with many different and sometimes antagonistic roles in mammalian physiology.

The understanding of the symptoms associated with abnormal Hia synthesis and reception has progressed thanks to the generation and characterization of HDC and Hia receptors knock-out (KO) mice. The lack of Hia production has remarkable systemic effects, including those on immune cell differentiation and response, tumour progression, alteration of the sleep-wake cycle, bone loss and fertility [15–17]. The phenotypic characterization of KO mice lacking the different Hia receptors has been of great help in identifying specific effects mediated by these GPCRs [18]. Several of the phenotypic alterations found in human diseases are believed to be associated with Hia signalling, and they will be discussed later in the text. The search and development of new and more specific modulators of these proteins is an active area of research and development (R&D) initiatives [9, 19, 20].

Rare diseases (RDs) are pathologies characterized by a very low prevalence (less than two patients per 1000 inhabitants in Europe), although almost 6000 of these conditions have been described (www.orpha.net). As there are only a few patients affected by each of these diseases, pharmaceutical companies express a general lack of interest in investing in drug development for these conditions. In the case of Hia, the modulators of its action could not only be taken into consideration for the treatment of RDs, but they are also useful for the treatment of more common diseases, as noted above [1, 9, 10, 19–21]. Thus, a question arises: for how many of these RDs is Hia a part of the problem? Hia has been clearly related to several RDs, including the following: histidinaemia [22]; mastocytosis and basophilic leukaemias [23]; Zollinger-Ellison syndrome; rare gastric carcinomas [24]; and in the development of inflammatory bowel diseases [25], among others. In fact, modulators of the Hia receptors have been proposed or are actually being used as part of current treatments against these pathologies.

As stated recently by Roubertoux and de Vries [26], RDs may share several common pathophysiological mechanisms with other diseases. Therefore, a discovery in one of them can have direct relevance to many others, especially in the case of non-monogenic RDs involving mutations affecting the complex protein-protein interaction networks of signalling pathways. In the elegant work published by Goh *et al.* [27] on the human disease network ('diseasome'), the authors were surprised by most disease-related genes being located in the periphery of the human interactome network. This means that these genes show poorer correlations between their expression patterns and those of the rest of the genes than expected from random, as they tend to be expressed only in a few tissues.

Hia-related genes have a lot of the most common properties of disease-related genes. Hia is a product of secondary metabolism, produced in a reduced set of cell types, and its effects are mainly elicited by different, tissue-specific signalling pathways. This fact should link this amine to multiple RDs involving cell-specific signalling mechanisms, as concluded from the diseasome analysis [27, 28]. However, a simple search for hits using the keywords 'histamine & rare/orphan diseases' in any bibliographic database (for example, Pubmed – http://www.ncbi.nlm.nih.gov/pubmed/), will only retrieve approximately 100 references, although there are many reasons to expect that Hia-related genes may be well represented and highly connected in a complete diseasome.

Systems Biology resources provide useful tools for producing new data through the integration of previous data fragments [29–31]. Hence, we have used a text mining approach to help us reveal the links between Hia-related factors and RDs, mainly inflammatory, neurological and neuroendocrine, and cardiovascular diseases, as well as rare tumours, for which consistent molecular/genetic together with physiological information is found.

Initial text mining approach

The data used to determine the relationship between Hia and RDs has been obtained using a biomedical literature mining approach and a subsequent experts' review. The first stage of the text mining analysis was completed with SciMiner [32], an online tool based on a dictionary- and rule-based biomedical literature mining analysis. A specific query was performed through SciMiner to identify PubMed Unique Identifiers (PMID) and genes associated with diseases and Hia. The specific query used Medical Subject Headings (MeSH) terms to ensure that the query will address the aims of our study. The MeSH terms belong to a controlled vocabulary following a hierarchical

structure where more general terms include the specific ones [33]. This resource has been widely used to index journal articles in Medline, books and journal titles [33–35]. We have selected 'Congenital, Hereditary, and Neonatal Diseases and abnormalities' (MeSH ID: D009358) as the broader term associated with genetic or hereditary diseases; and 'Histamine' (MeSH ID: D006632) to link our query with the right molecular pathway.

From the literature mining analysis, we gathered 382 genes in 1419 PMIDs. These genes represent a global genetic background of diseases involving Hia. This is the global genetic background used to annotate genetic RDs associated with those genes using the information annotated in the Orphanet database. For each gene, we counted the number of papers that cited it and the total gene-RD co-occurrences. This method serves as an estimate of the contribution of each gene related to RDs to the results. As a result, we obtained 211 RDs related to 140 genes in the global genetic background. In addition, a functional enrichment analysis based on a Fisher's exact test was used to value more representative and statistically significant MeSH terms annotated within papers retrieved from the biomedical literature mining analysis.

However, to identify the most significant results among the collected data, we isolated genes and their associated RDs directly annotated to the 'Histamine' MeSH term. From this last search, we obtained 20 genes that were also present in the first broader search process. We prioritized them according to the number of cited papers and the total occurrence, and then we performed a manual curation of the results. In this review, we include results for which there is a clear relationship between one or more components in the Hia signalling network and the molecular and phenotypic aspects of a specific RD.

With the text mining tools described previously, we have been able to identify different types of interrelationships between genes involved in Hia metabolism and genes encoding for proteins directly correlated with the appearance and development of several RDs. Table 1 includes the list of these RDs, together with the Orphanet and OMIM (http://www.ncbi.nlm.nih.gov/omim) identification codes and at least, a representative reference.

Histamine and inflammation/immune system-related RDs

The immune response is a highly multifactorial process. Hence, it is almost impossible to accurately determine how many diseases are related to or are dependent on the immune/inflammatory response. Furthermore, there are multiple pathologies involving inflammation that are not traditionally treated as inflammatory diseases, so there is not a solid classification of these conditions. If we focus on RDs, there are approximately 200 RDs that are related somehow with the immune system, representing approximately 3.2% of the RDs indexed in the Orphanet database, although this value is most likely underestimated.

The proinflammatory effects exerted by Hia seem to be elicited mainly through H_1R and H_4R. H_1R, expressed by endothelial cells and smooth muscle cells, mediates vasodilation and bronchoconstriction associated with multiple inflammatory responses. On the other hand, H_4R is mainly expressed in cells of hematopoietic origin, in particular dendritic cells, mast cells, eosinophils, monocytes, basophils and T cells. H_4R demonstrates a higher affinity for Hia compared with H_1R, and it also promotes Ca^{++} mobilization and activates MAP kinase-dependent signalling pathway [9, 36]. H_4R is therefore considered to be the coordinator of immune system communication in response to Hia.

Hia levels are increased in bronchoalveolar fluids extracted from allergic asthma patients, in the skin and plasma of patients with atopic dermatitis, in chronic urticaria biopsies, in both plasma and synovial fluid of patients with rheumatoid arthritis and in the plasma of patients with psoriatic arthritis. These observed phenomena occur because the antihistamines that are currently used in the clinic have little, if any, affinity for H_4R. Thurmond *et al.* [9] suggest that there is a need to develop better H_4R modulators to revisit the potential of antihistamines against inflammatory diseases, including the newly identified ones. Lots of different research groups are working towards achieving a complete biochemical and pharmacological characterization of this novel Hia receptor [10, 37, 38].

Cryopyrin-associated periodic syndrome (CAPS) comprises a group of inflammatory diseases associated with a mutation in the NLRP3 gene (NACHT, LRR and PYD domains-containing protein 3) that include the following: familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease, formerly known as chronic infantile neurological cutaneous articular syndrome. CAPS is characterized by a neurological condition, articular symptoms, a skin urticarial rash and chronic inflammation. The NLPR3 gene encodes for the protein cryopyrin, a component of the inflammasome, which is a multiprotein complex that mediates the innate immune response [39]. In the skin of CAPS patients, mast cells produce interleukin 1β (IL-1β) in a constitutive manner (Fig. 1A). This is in contrast with normal mast cells, which produce IL-1β only in response to proinflammatory stimuli. Increased IL-1β production has also been observed in monocyte-derived dendritic cells in CAPS patients [40]. According to the information provided by Orphanet, lots of anti-inflammatory drugs have failed in palliating the symptoms accompanying these syndromes. Inhibition of IL-1β production leads to a reduction of the inflammation observed in the patients. Recent results show that the H_4R antagonist JNJ7777120 decreased the expression of IL-1β mRNA in murine dendritic cells [41]. The expression of many other immune mediators (IFN-γ, IL-6, IL-10, etc.) can also be modified by signalling activation or repression through H_4R in these dendritic cells.

Systemic juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease characterized by articular disorders and immunoregulatory abnormalities. Severe cases of systematic JIA result in macrophage activation syndrome, which presents an excessive activation and proliferation of T cells and macrophages. During the active phases of JIA, patients display an abnormally high rate of interleukin 6 (IL-6) production [42] (Fig. 1B), and these elevated IL-6 levels correlate with the daily fever peaks suffered by JIA patients. A polymorphism found in the promoter of IL-6 gene has been thought to be responsible for the overproduction of this cytokine [43]. IL-6 is a crucial cytokine for mast cell maturation and it upregulates Hia release rather than increasing its

Table 1 Rare diseases related to histamine signalling and/or metabolism

Disease	Mutated gene/origin	Orphanet ID	Omim ID	Reference
Immune/Inflammatory RDs				
Psoriatic arthritis	HLA-C, NOD/CAR15, TNFA, LTA	40050	607507	—
Idiophatic aplastic anaemia	TERC, TERT, IFNG,NBS1, PRF1, SBDS	88	609135	[49, 50]
Familial cold autoinflammatory syndrome	NLPR3	47045	120100	[39, 40]
Muckle-Wells syndrome	NLRP3	575	191900	[39, 40]
Infantile neurologic cutaneous articular syndrome	NLRP3	1451	607115	[39, 40]
Systemic juvenile idiopathic arthritis	IL6, MIF	92	604302	[42, 43, 46]
Crohn's disease	NOD2/CAR15, IL6	206	266600	[53, 54]
Ulcerative colitis	Autoimmune	771	266600	[53, 54]
Neurological RDs				
Narcolepsy with cataplexy	HCRT	2073	161400	[63, 64]
Tourette's syndrome	HDC, SLITRK2	856	137580	[65]
Hereditary essential tremor	DRD3, ETM2, ETM3	862	190300	[75]
Myoclonic dystonia	DRD2, SGCE	36899	159900	[76, 77]
Neuroinflammatory RDs				
Myasthenia gravis	Autoimmune	589	159400*	[83, 86]
Hereditary sensory and autonomic neuropathy, type IV	NTRK1	642	256800	[85, 87]
Hereditary sensory and autonomic neuropathy, type V	NGFB	64752	608654	[85, 87]
Multiple sclerosis	HLA genes on 6p21, MS2, MS3, MS4	802	126200	[89–91]
Rare neoplasias				
Acute myeloid leukaemia	Heterogeneous	519	252270	[97]
Zollinger-Ellison syndrome	Sporadic/associated to MEN1 mutation	913	131100	[99]
Mastocytosis	cKIT, TET2	98292	154800	[23, 100–105]
Other RDs				
Vitamin D-dependent rickets type 2A	VDR	437	277440	[110]
Familial long QT syndrome	Potassium voltage-gated channels	768	152427	[112]
Brugada syndrome	Ionic voltage-gated channels	130	601144	[113]
von Willebrand disease	VWF	166078	193400	[114–17]
Metabolic syndrome	Heterogeneous	68367	–	[118]
Congenital adrenal hyperplasia	Heterogeneous	418	145295	[119]
Histidinaemia	HAL	2157	235800	[22, 122]

The position of each disease in the table follows its order of appearance in the text. Under the 'mutated gene/origin' column, the reported causes of the different rare diseases are indicated.

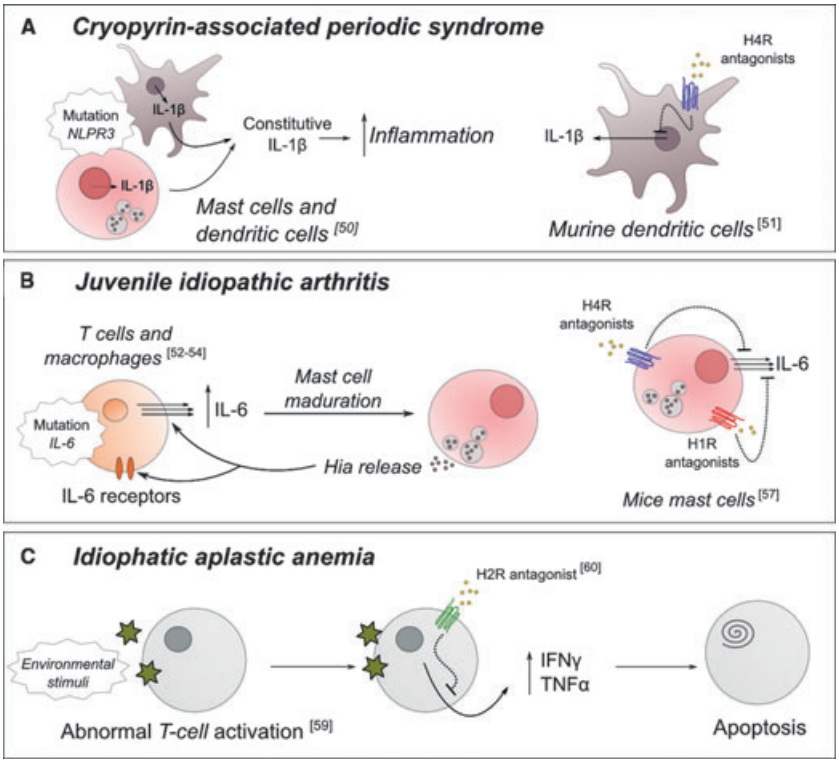

Fig. 1 Schematic representation of the reported role of histamine-related factors in three of the inflammatory rare diseases mentioned in the text. For cryopyrin-associated periodic syndrome and juvenile idiopathic arthritis, the experimentally validated inhibitory mechanism in non-human cells is also depicted. Representative references are provided.

storage [44]; reciprocally, Hia stimulates both IL-6 production and expression of IL-6 receptors on different cell types, such as human lymphoid, monocytoid and hepatoma cell lines [45]. There are some reported cases in the literature regarding JIA patients who presented an increased number of mast cells in the gastric and duodenal mucosa or elevated levels of urinary Hia [46]. Desai and Thurmond have reported on Hia's role in regulating both IL-6 production and mRNA expression in mice mast cells *via* H_4R activation [47]. At the same time, this production was shown to be blocked by two H_4R antagonists, JNJ 7777120 and JNJ 28307474; partially blocked by H_1R antagonists; and not blocked by H_2R or H_3R antagonists. Furthermore, there was no Hia-dependent IL-6 production in H_4R-deficient mice. At the same time, H_4R antagonists have already been used for *in vivo* tests, showing a reduction of IL-6 levels in asthma [48]. As far as we know, the potential usefulness of this relationship for preventing the development of JIA has not yet been explored.

There is also evidence for a role for H_2R in regulating Hia synthesis and cytokine production in immune cells, and consequently, it may be implicated in immune abnormalities developed in certain RDs. For instance, the RD idiopathic aplastic anaemia is characterized by a disturbed immune system, usually associated with abnormally activated T lymphocytes, leading to high levels of suppressive cytokines, such as IFN-γ and TNF-α [49] (Fig. 1C). These cytokines prevent stem cells in the bone marrow from differentiating and can even induce stem cells to undergo apoptosis. H_2R is expressed in T lymphocytes, and cimetidine, its antagonist, modulates the function of these cells by not fully characterized mechanisms. It has been demonstrated that treatment with cimetidine leads to a reduction in the production of both cytokines, IFN-γ and TNF-α, and partially reverses their haematopoietic suppressive effect in aplastic anaemia in mice [50]. Thus, the antagonist cimetidine could be an appropriate treatment for patients of this RD. Like H_2R, H_4R expression has also been found in several T cell types [36, 51]. For instance, it has been observed that in HDC KO mice, there is a drastic decrease in the production of IFN-γ by natural killer T cells. This is reversed by a single injection of Hia, and this process is mediated by H_4R [52]. It would be of great interest to determine whether H_4R-mediated IFN-γ production occurs in other T cell types, because the use of H_4R antagonists could be useful for the modulation of cytokine overproduction in idiopathic aplastic anaemia patients.

Crohn's disease and ulcerative colitis are rare inflammatory bowel diseases in which Hia produced by mast cells plays an important role. Patients with these conditions show an increased level of Hia excreted in the urine, which correlates with the clinical manifestation of this disease [53]. It has been suggested that mediators released from Hia-expressing cells in the intestine could be responsible for the progression of these diseases. Hia activity through H_1R mediates inflammatory effects, whereas H_2R and H_4R signalling trigger the production and secretion of immune mediators, such as cytokines. Furthermore, Hia is involved in the preferential activation of Th2 cells, which promote further inflammatory effects that can lead to the appearance of intestinal infections and tumours. Several authors have also proposed the clinical use of H_4R antagonists as promising anti-inflammatory effectors [54].

All these findings together suggest a promising future for further development of new modulators of the Hia synthesis and signalling in the treatment of this group of RDs and other more prevalent inflammatory/immune diseases.

Histamine and rare neurological disorders

There are 1937 RDs related to some neurological abnormality. This is over 30% of all the RDs indexed to date. Over 60,000 neurons localized in the hypothalamic tuberomammillary nuclei are the major source of Hia produced in the brain [12, 55]. The histaminergic system is involved in the development of very different functions in the CNS (wakefulness, appetite control, learning and memory, stress, etc.) [56], and all these physiological functions are mediated through H_1, H_2 and H_3 receptors [12]. H_1R is located in most brain regions, and Hia exerts neuroendocrine, behavioural and nutritional control through it. H_2R in the brain mediates postsynaptic functions of Hia related to cognition, nociception and immune function. Due to their colocalization in some regions of the brain, H_1R and H_2R could carry out synergistic effects [12]. H_3R regulates the synthesis and release of Hia from histaminergic neurons through a negative feedback mechanism [57] and controls the release of some other neurotransmitters, such as the biogenic amines glutamate, gamma-aminobutyric acid and acetylcholine. The presence of H_4R in different regions of the CNS has already been demonstrated, although its specific functions and protein-protein interactions are not yet fully elucidated [14]. The first studies in this field are currently being published [58].

During the sleep-wake cycle, higher levels of Hia have been reported when the organism is awake than when sleeping [59]. Wakefulness is mediated by Hia in conjunction with orexins and hypocretin [60, 61], and both systems are located in close proximity. Nevertheless, orexin neurons control motor-related functions, including posture, muscle tone and food intake, whereas the Hia system controls cognitive activities when the organism is awake [62]. Therefore, both systems are responsible for distinct, but complementary tasks during wakefulness. The autoimmune sleep disorder narcolepsy with cataplexy is caused by a loss of hypocretin-producing neurons in the brain [63]. In zebrafish, several studies of the interaction of the two systems have revealed that low levels of Hia, either by the use of HDC inhibitors or by the use of HDC KO fish, lead to a reduction in hypocretin neurons and this effect is mediated by signalling through H_1R [61]. In humans, this phenomenon has been observed for years in the sedative effects exerted by first generation antihistamines that target H_1R. Hia has also been connected to sleep regulation through H_3R. In fact, several H_3R antagonists are in clinical development not only for cognitive enhancement but also for the treatment of narcolepsy and cognitive deficits [64]. In Orphanet database, there are 29 diseases related to sleep-wake cycle abnormalities, and 79 genes are associated with these conditions. Due to its important role in wakefulness, we propose that Hia metabolism and signalling genes should be sequenced in patients with these RDs. This could contribute to the development of new personalized medicine treatments. We are confident that the proposed effort will reveal the molecular mechanisms involved in the development of these RDs.

The histaminergic system is also implicated in Tourette's syndrome, a developmental neurological disease characterized by chronic motor and vocal tics along with other psychiatric symptoms. In a recent study comprised of several members of the same family, it was observed that each family member presented a premature termination codon in the HDC gene at the position coding for residue 317 [65]. Our group have generated and validated the first structural model of the active conformation of mammalian HDC [2, 3]. In this truncated version, the enzyme lacks important residues involved in the formation of the binding pocket and the establishment of the proper catalytic environment, leading to a decrease in the production of Hia in the CNS. These symptoms can be mimicked in HDC KO mice, which demonstrate enhanced locomotor behaviour after treatment with dopamine agonists, such as metamphetamine (discussed below). A novel treatment for these motor-related symptoms requires an increase in histaminergic neurotransmission, achievable by the use of selective antagonists of the autoreceptor H_3R [66]. Even when HDC activity does not seem to be the only cause of the motor tics in all Tourette's syndrome patients [65], the putative influence of distinct Hia-related elements in this pathology is an interesting open field of study.

Hia system is closely linked to dopamine metabolism and signalling in the brain (Fig. 2A). The histaminergic system enhances its activity *via* D_2 receptor when dopamine agonists (L-dopa for example) are administrated [67]. Methamphetamine (MET) is an antipsychotic drug used by schizophrenia patients that stimulates locomotor activity and has been extensively used in the medical field to simulate psychosis and schizophrenia in animal models [68, 69]. MET stimulates the release of dopamine and Hia, the latter stimulated by endogenous dopamine acting on the D_2 receptor. MET also stimulates HDC activity in localized parts of the CNS [70, 71]. When MET is administered, both hyperactive locomotion and an increase of Hia levels are observed. However, enhanced locomotor activity reaches its maximum peak just a short time after administration, correlated with the maximal dopamine concentrations. The enhanced motor activity then rapidly decreases, whereas the levels of Hia metabolites continue to increase for several hours. Hence, it has been proposed that the histaminergic system is involved in the inhibition of the response due to MET and this effect is mediated by dopamine and D_2 receptor. This assumption was further corroborated with H_3R antagonists that increase the release of Hia in the brain, leading to an overall decrease in the motor alterations exerted by MET [72]. This relationship has also been found in the early stages of life. The use of MET in prenatal and young mice has shown that Hia mediates the harmful effects that MET has on their developing brain, and the appearance of these effects can be avoided by treating them with the H_3R agonist imepip [73]. The administration of MET results into abnormally high levels of Hia in the CNS during the first stages of mice development, resulting into long-term detrimental cognitive functions in the adult. In human children, the exposure to MET in the prenatal stage leads to the reduction of

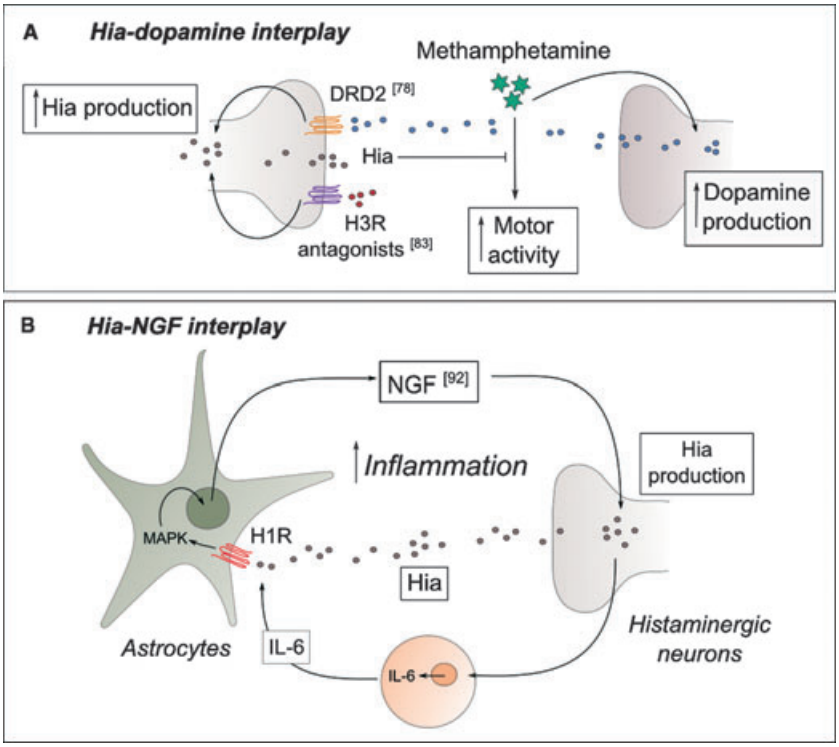

Fig. 2 Schematic representation of the interplay between histamine-related factors and both dopamine and nerve growth factor (NGF). HDC, histidine decarboxylase; DRD2, dopamine receptor D_2; MAPK, mitogen-activated protein kinase. Representative references are provided.

several brain structures and cognitive impairments related to attention, verbal and spatial memory [74].

Several RDs are characterized by malfunctions of the locomotor system, such as dystonia or ataxia. The D_3 dopamine receptor has been traditionally associated to hereditary essential tremor [75]. However, controversial results have been published concerning the role of D_2 dopamine receptor in the development of the RD myoclonic dystonia [76, 77]. Taking into account the data presented above, there is evidence suggesting that the histaminergic system may play an important role in the development and modulation of symptoms involving the motor system. There is experimental evidence of the physical interaction between dopamine D_1 and D_2 receptors and H_3R when they are located in the postsynaptic membranes of certain brain cells [78, 79]. The regulation of the signal through these heteromers has been demonstrated to be significantly different from what occurs in the separated receptors. These physical interactions are excellent proof of the close relationship existing between dopaminergic and histaminergic neurotransmission systems.

In 2008, Ledesma and collaborators reported the linkage of a non-synonymous polymorphism in the enzyme histamine N-methyltransferase to an increased risk of developing essential tremor [80]. This enzyme is responsible for part of the Hia degradation, so alterations in its function may lead to unbalanced levels of Hia. Nevertheless, two independent groups have recently found opposing results to those of Ledesma and coworkers in patients with essential tremor, Parkinson's disease and Alzheimer's disease [81, 82]. It is possible that the alterations in different Hia-related elements could cause a phenotypic convergence in these pathologies, whose symptoms comprise both locomotor and/or cognition alterations.

Histamine and rare neuroinflammatory diseases

There are a significant number of neurological diseases that are also characterized by inflammatory symptoms; therefore, we are dedicating a separate section for the discussion of these diseases. In our text mining study, Hia has been linked to nerve growth factor (NGF), a homodimeric protein that acts as a mediator of inflammation in injured tissues, induces neuronal differentiation, promotes neuronal survival and prevents apoptosis in neurons of both central and peripheral nervous systems. It exerts its function through the neurotrophin tyrosine kinase receptor type A (TrKA) and the p75NTR receptor for neurotrophins [83–85]. Most inflammatory cells in humans express both TrKA and p75NTR receptors, and this expression is increased in certain inflammatory diseases, such as atopic dermatitis and myasthenia gravis (a rare autoimmune neuromuscular disorder) [83, 86]. Mutations in the genes encoding for TrKA and NGF have been linked to the rare neuropathy hereditary sensory and autonomic disease types IV and V respectively [85, 87]. These pathologies are characterized by loss of pain perception, mild mental retardation and immune deficiency. All these symptoms occur with varying severity. Whilst it has been demonstrated that TrKA expression is Hia-independent [88], this amine is

a powerful stimulator of NGF production, and the main signalling pathway involved in its synthesis and secretion in the CNS includes H_1R activation [45, 83] (Fig. 2B). Moreover, NGF enhances the production and release of Hia. The positive feedback loop between these two factors leads to a substantial increase in the inflammatory response, which promote more severe symptoms in many inflammatory diseases. To control this process, several H_1R antagonists have been used in the treatment of skin inflammatory conditions [83]. Besides its direct stimulation of NGF production, Hia is able to indirectly stimulate it together with different cytokines, such as IL-6 [45].

Different types of sclerosis are classified as RDs, and multiple sclerosis (MS) being the most studied. In MS patients, the myelin sheaths around the axons of nerve cells within the brain and spinal cord are damaged, leading to demyelination. As a result, there is impaired signal transmission in the affected nerves, causing a wide variety of symptoms. Mast cells, the main Hia producers, are involved in the onset of this disease through the release of inflammatory intermediates and the activation of T cells at the blood-brain barrier [89]. In a recent review by Jadidi-Niaragh and collaborators [90], the importance of Hia and its receptors in MS is discussed in depth. According to these authors, Hia would play a key role in regulating the pathogenesis of MS by promoting the differentiation of the T helper cell population to Th2 subgroup instead of the Th1 subgroup, leading to less severe symptoms, and by acting on oligodendrocytes and the remyelination process. Furthermore, several H_1R antagonists have been shown to ameliorate the symptoms of experimental MS models [90, 91]. Due to its localization in the brain, H_4R has been the focus of studies intending to determine its function in neuroinflammation.

Histamine and rare neoplasias

Hia and several elements of its metabolism are also directly related with tumour progression and angiogenesis in different types of cancer, including haematologic, breast, pancreatic, melanoma and colon cancer, as recently reviewed by Medina and Rivera [92]. Of course, both, cancer origin (gene-disease relationships) and cell-specific signal transduction mechanisms elicited by Hia, are diverse and multifactorial. As a consequence of this diversity, both growth-promoting and antineoplastic effects have been described for Hia in tumour cells of different origins.

An inflammatory environment is crucial in the development of malignant neoplasias. Immature cells in the myeloid linage (iMCs) are essential to tumour establishment and progression since they are able to avoid the cytotoxic response exerted by T lymphocytes and by negatively regulating the immune response [93, 94]. Under cancerous conditions, iMCs are localized within tumours and in their periphery; they are unable to synthesize Hia due to a disruption in the HDC gene [95]. HDC KO mice are more susceptible to chemically induced skin and colon cancer, so Hia seems to be effective in restricting tumour growth. Furthermore, Hia has been shown to exert inhibitory function in the development of many other types of experimental cancer (see the references in [96]). Nowadays, a treatment combining IL-12 and Hia is used to prevent relapse in acute myeloid leukaemia by the activation of cytotoxic lymphocytes [97] and by blocking the generation of reactive oxygen species, and hence protecting NK and T cells from apoptosis, in patients with renal cell carcinoma [98].

Zollinger-Ellison syndrome is a severe disease in which gastric acid secretion is over five times the upper normal limit, arising from the presence of a neuroendocrine gastrinoma. Several H_2R antagonists have been used to reduce this gastric acid hypersecretion [99].

Hia overproduction has also been associated with mastocytosis, a RD characterized by an abnormal accumulation of mast cells in different tissues [23, 100]. When released, the mediators of mast cells account for the majority of the symptoms associated with the disease and can even lead to death. Urine methylhistamine (a Hia metabolite) levels and HDC expression are considered markers in the diagnosis of this condition [101]. Nowadays, H_1R and H_2R antagonists are used in the treatment of skin and gastric ailments experienced by mastocytosis patients respectively [102]. Moreover, H_1R antagonists terfenadine and loratadine have been shown to inhibit the *in vitro* proliferation of neoplastic mast cells and induce apoptosis in a dose-dependent manner [103]. The activating mutation D816V in the c-Kit/stem cell factor is found in most mastocytosis patients [104]. Although the structural changes in c-Kit caused by the mutation have recently been predicted [105], we are far from fully understanding the alterations in the signal transduction cascade that lead to Hia synthesis/storage deregulation in these cells.

Histamine and other RDs

In several studies, Hia has been shown to increase the number and activity of osteoclasts (the cells responsible for bone resorption) [106]. HDC KO mice, which virtually lack Hia, have an increased rate of bone formation, increased cortical bone thickness and a reduced rate of bone resorption [107]. On the one hand, significantly higher levels of Hia are found in patients with osteoporosis and mastocytosis [108]. Hence, it has been proposed that specific inhibitors of Hia production or signalling could be used to counter the effects observed in these conditions [108, 109].

Mutations in the vitamin D3 receptor (VDR) gene have been found to be the cause for the rare disease vitamin D resistant rickets, characterized by an increased rate of circulating vitamin D3 and physical defects, such as the aberrant mineralization of cartilage and bones. In normal osteogenesis, VDR acts as a transcription factor, and one of its downstream targets is H_1R [110], whose levels are increased in cells overexpressing VDR. Pochampally and collaborators determined that mineralization was promoted *via* H_1R, but not H_2R, in cells expressing VDR. However, Hia was not able to significantly increase osteogenesis, although H_1R antagonists are able to inhibit the differentiation of bone cells, suggesting the existence of unknown H_1R interactions. Therefore, H_1R-mediated signalling, independent of Hia, must be involved in bone construction/destruction equilibrium. However, there is no doubt that this is a complex problem that needs further molecular characterization.

On the other hand, Hia has also been found to be involved in several cardiovascular conditions. In heart, the response to Hia is mediated by H_1R and H_2R, which resemble the functions exerted by

the adrenergic system receptors [111]. H_1R antagonists are known to block HERG1 potassium channels, so they delay the action potential repolarization and prolong the QT syndrome [112]. Besides, the activation of H_2R by Hia produces a positive ionotropic effect in the heart. There are several RDs characterized by a prolongation of the QT interval, syncope, arrhythmia and cardiac failure. A recent example in the literature shows that several H_1 antihistamines have been found to deteriorate one of the symptoms associated with Brugada syndrome, a cardiac RD [113].

The von Willebrand factor (VWF) is a glycoprotein present in plasma that plays an essential role in platelet adhesion and thrombosis. A deficiency in the level and/or quality of VWF leads to the so-called von Willebrand disease, comprised of at least seven types, which are mainly characterized by different coagulation abnormalities [114]. VWF can be released either constitutively from endothelial cells or from storage granules, called Weibel-Palade bodies. VWF release is mediated by an increase in intracellular Ca^{++} induced by Hia through H_1R [115, 116]. Dopamine, through its receptors D2, D3 and D4 can inhibit Hia-mediated VWF release, but this effect is not mediated by Ca^{++}-dependent signalling; hence, the biochemical aspects of this inhibition still remain unknown [117]. This is an additional example of the complex network surrounding this biogenic amine.

Hia is also playing a key role in metabolic disorders by triggering the inflammatory response and by taking part in the modulation of the metabolism [118]. Fatty liver syndrome and its related severe condition, namely non-alcoholic steatohepatitis, is associated with obesity, insulin resistance and inflammation, among other symptoms. The implication of Hia in these syndromes, and more precisely, its action through H_1 and H_2 receptors, have been proven to be of great importance in the regulation of glucose and lipid metabolism.

Congenital adrenal hyperplasia comprised a group of syndromes involving abnormalities in the production of adrenal hormones, due to the deficiency of different enzymes of the cytochrome P450 superfamily [119]. Adult patients are often obese and present bone and metabolic abnormalities, as well as fertility problems. This cytochrome is the known target for multiple biogenic amines including Hia, which regulates the catalytic activity of these enzymes and cell function by binding them on specific sites [120]. Not only is Hia known to bind cytochrome P450 enzymes but also several H_3R antagonists [121].

On the other hand, patients with histidinaemia, a benign disorder caused by a defect in the enzyme histidine ammonia-lyase, responsible for the conversion of histidine into ammonia, show an increased Hia metabolism [122]. Recently, it has also been observed that a mild chronic homocysteinemia leads to increased HDC expression and macrophage infiltration in mouse liver. These findings can be interesting for homocystinuria patients [123].

Insights for new translational initiatives

This review points out some connections between RD-related elements and Hia-metabolism/signalling related factors. This provides insights for deeper characterization of the underlying molecular mechanisms of these pathologies and for new intervention strategies. We are convinced that this approach will become progressively more informative as human interactomes and diseasomes [27, 28] are enriched and properly curated.

It is obvious that the recent discovery of H_4R and its ubiquitous location, together with its key role in the regulation of the immune response, has forced researchers to revisit the previously collected data on the effects exerted by Hia [9]. Thus, new translational initiatives require a better molecular characterization of the H_4R-mediated responses and the development of new H_4R-specific ligands [20, 124].

The data presented in this review demonstrate a clear interplay (including physical interactions) between Hia and dopamine metabolism/signalling-related factors. Their implication in several rare neurological diseases, primarily those affecting motor functions, suggests that they will be key targets for pharmacological intervention [57].

Another possibility for therapeutic intervention in these Hia-related RDs might be to take advantage of the previously reported properties of natural compounds, some of them cheap and easy to bring to the clinical testing phase [125, 126]. In this type of compounds, tea polyphenols are one of the most noteworthy [127]. Epigallocatechin-3-gallate (EGCG), the most abundant polyphenol in green tea leaves, has been described as an antioxidant [128, 129], antiangiogenic [130], antiproliferative [131–133] and anti-inflammatory compound [134, 135]. In 2003, Rodríguez-Caso *et al.* demonstrated a direct inhibition of HDC activity by EGCG. In the last few years, knowledge about the physiological and molecular effects of EGCG has increased enormously, as has its demonstrated positive effects in the treatment of several diseases [136–138]. Some of the Hia–related genes mentioned in this review are known to be targets of EGCG. For example, Gundimeda *et al.* [139] demonstrated that EGCG potentiated NGF-induced neurite outgrowth. As EGCG can cross the blood-brain barrier, these authors propose that this compound can be a highly useful tool in the treatment of neuronal injuries. EGCG also inhibits IL-6 secretion [140], and the relationship of IL6 with Hia and NGF secretion has already been mentioned before. Consequently, the connection between EGCG and all these factors as well as their consequences on RDs deserves further attention as it may have translational potential. Another application for EGCG may be to use its potential as a preventive agent in combined therapies against skin inflammatory diseases, such as mastocytosis [23, 127]. EGCG has already been used in the treatment of non-rare skin inflammation [141–143].

Concluding remarks and proposed future actions

Here, we present evidence that suggests the involvement of different Hia-related factors in more than 25 RDs, most of them inflammatory and neurological diseases. The initial search for connection between Hia and RDs was performed with text mining tools, followed by a manual curation of the retrieved data. Our observations reveal several

new points of discussion on each topic and suggest several valuable lines of action for the near future. They indicate a need for further R&D efforts to advance the topic¸ supporting the idea that research on RDs can efficiently progress towards translational applications by combining computational and experimental approaches (including high-throughput and post-genomic technologies among others) and clinical information.

Several RDs are associated with polymorphisms in Hia-related proteins. In our opinion, these data only represent the beginning of the potential knowledge on this topic. The characterization of the exome and transcriptome of RD patients should reveal further relationships among Hia-related gene polymorphisms and RDs, which can help advance the goal towards personalized therapies. Fortunately, KO animals have been developed for most of the Hia metabolism/signalling-related genes, and many experimental animal models also exist for many RDs. Collaboration between clinical and basic research groups could provide critical information about the systemic effects of alteration of these Hia-related factors. These efforts, together with high-throughput post-genomic technologies and biocomputational analysis (systems biology-associated technologies), will accelerate the process and will help patients afflicted with many different RDs.

Many modulators of Hia receptors have been described and used in therapies against a wide range of pathologies. As for the newest Hia receptor, H_4R, it is crucial to discover its structure and its interacting partners in different cell types, taking into account the possibility that it generates dimers with other receptors (for example, dopamine receptors). This information can provide new methods for interfering with the relevant roles of H_4R as coordinator of immune cell communication not only in RDs, but in the full diseasome. A European Science Foundation initiative (COST Action BM08/06) includes action towards these objectives.

A handicap in the development of novel drugs against RDs is the high cost of investment compared with the number of potential drug consumers. That will not be the case for Hia modulators, because they would have a wide range of applications in many emergent inflammatory, neurological and gastrointestinal diseases. In fact, as we still do not have a full view of the human diseasome, the information collected in this review leads us to suggest that Hia-related factors must be directly connected to, or at least take part in, the signalling networks of many different diseases.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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