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Commentary

The therapeutic potential of histamine receptor ligands in inflammatory bowel disease☆

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ABSTRACT

In the intestine of patients suffering from inflammatory bowel disease concentrations of histamine are increased compared to healthy controls. Genetic ablation of histamine production in mice ameliorates the course of experimentally induced colitis. These observations and first pharmacological studies indicate a function of histamine in the pathogenesis of inflammatory bowel disease. However, a closer examination reveals that available data are highly heterogeneous, limiting the rational design of strategies addressing specific histamine receptor subtypes as possible target for pharmacological interaction. However, very recently first clinical data indicate that antagonism at the histamine receptor subtype H_4 provides a beneficial effect in at least the skin. Here, we discuss the available data on histamine effects and histamine receptor subtype functions in inflammatory bowel disease with a special emphasis on the histamine H_4-receptor.

1. Introduction

There is current interest in the role of histamine in the pathogenesis of inflammatory bowel disease. Evidence for this interest is documented by a recent review entitled "*Histamine and Gut Mucosal Immune Regulation*" [1]. Histamine is recognized by target cells via four receptor subtypes (histamine H_1-receptor (H_1R)–H_4R), which all seem to be involved in histamine effects in gastrointestinal disorders [2]. Thus, one could hypothesize that targeting histamine receptors represents a promising strategy for the therapy of inflammatory bowel disease. Unfortunately, pharmacological aspects of such intervention have not been addressed adequately in the review by Smolinska et al. [1]. Consequently, the purpose of this commentary is to critically review studies analyzing the function of histamine and histamine receptors in models of inflammatory bowel disease. We will discuss the feasibility of currently available histamine receptor ligands as possible therapeutics, placing an emphasis of the commentary on the H_4R, since accumulating evidence is pointing toward an important role of the H_4R in inflammatory diseases such as allergic asthma and dermatitis, experimental autoimmune encephalomyelitis, or arthritis [3,4] and probably also inflammatory bowel disease [5]. Therefore, H_4R antagonists are currently 'hot candidates' in the development of new anti-inflammatory drugs and some of them have already been submitted to clinical trials [6–8]. However, while the involvement of histamine in inflammatory diseases of the gut is well documented, data directly proofing a function of the H_4R are sparse. This may be due to the complex pharmacology of some H_4R ligands [9,10], which we will discuss in detail.

1.1. Inflammatory bowel diseases

IBD is a growing health problem with continued lack of causal pharmacotherapy. The two main types of IBD are ulcerative colitis (UC) and Crohn's disease (CD), which can be clearly distinguished from each other by clinical, histopathological, endoscopic, and radiological parameters [11,12]. UC is a chronic inflammation of the colonic mucosa, which, ascending from the rectum, may spread throughout the entire colon, but eventually remains limited to it. Formation of ulcers may occur, resulting in blood, pus, and mucus

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Abbreviations: H_XR, histamine receptor subtype X; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; TNF, tumor necrosis factor; JNJ 7777120, 1-[(5-chloro-1*H*-indol-2-yl)carbonyl]-4-methylpiperazine; DSS, dextran-sulfate sodium; TNBS, 2,4,6-trinitrobenzene sulfonic acid; GPCR, G protein-coupled receptor; IL, interleukin; MPO, mucosal myeloperoxidase; HDC, L-histidine decarboxylase.

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in the stool. CD is a chronic inflammatory process in which all layers of the wall of the whole digestive tract, from the mouth to the anus, can be affected. The spread is irregular; healthy and inflamed sections alternate and there is a tendency to fistula and abscess formation [11,13–15]. Furthermore, patients with IBD have an increased risk for the development of colon cancer [16] and extraintestinal manifestations such as arthritis, osteoporosis, and sacrolitis [13].

The onset of UC and CD usually takes place in adolescence or young adulthood with a multifactorial pathogenesis [14]. Currently it is assumed that a complex interplay of genetic, microbial and environmental factors leads to an inappropriate and excessive activation of the intestinal innate immune system and, as a result of it, even to that of the adaptive immune system [11,17–20], which is commonly referred to as 'loss of oral tolerance'. The increase in incidence of IBD observed in recent decades cannot be attributed to a genetic drift in the population, but to changes in environmental factors such as an altered eating behavior [21].

Neither UC nor CD can currently be cured. Aim of the applied drugs is merely to reduce inflammation and to prevent exacerbations, thus improving the patient's quality of life. Acute attacks are treated with anti-inflammatory drugs such as 5-aminosalicylic acid or corticosteroids, or, if the response is inadequate, with immunosuppressive agents or tumor necrosis factor (TNF)-antibodies. However, the remission rates of these therapies are only about 50% [22]. In addition, patients under chronic therapy have a greatly enhanced risk of developing immunosuppressive-dependent cancers or lymphomas or to suffer from opportunistic infections [23,24]. Thus, there is a high medical need for new IBD therapeutics, including immuno-modulatory ones, preferentially leading to enhanced remission rates in combination with a reduced risk of severe side effects.

1.2. Histamine

The biogenic amine histamine (2-(4-imidazolyl)-ethylamine) is an endogenous mediator that is derived from the amino acid L-histidine via catalysis by the enzyme histidine decarboxylase (HDC). Histamine is formed primarily by mast cells and basophils and occurs in virtually all tissues, at least of the mouse [25]. It is involved in a variety of biological processes such as inflammation, the regulation of gastric acid secretion, and neurotransmission [26]. Recognition of histamine by its target cells is mediated by four different receptor subtypes (H_1R–H_4R). Histamine receptors belong to the family of 7-transmembrane, so-called G-protein coupled receptors (GPCRs). The main proximal signaling events are the mobilization of intracellular calcium by H_1R and H_4R, the increase in the intracellular cAMP concentration by H_2R, and the reduction of intracellular calcium and cAMP levels by the H_3R.

1.3. Histamine receptors in the immune system

While the H_3R is almost exclusively found in the nervous system, H_1R and H_2R are expressed ubiquitously, including immune cells [27]. The H_4R is expressed predominantly by cells of the immune system, so far it was clearly detected on mast cells, eosinophils, T cells and dendritic cells [3,26–30]. However, the proposed exclusivity of its expression on immune cells is subject of current debate [31,32]. On immune cells the H_4R modulates migration and activation of eosinophils and mast cells [29,30] and activation of dendritic cells and T cells [28,33–35]. Accordingly, it was also shown that genetic or pharmacological blockade of the H_4R function in various models of inflammatory diseases leads to significantly improved symptoms [36–39].

1.4. H_4R expression on non-hematopoietic cells

Several reports indicate that the H_4R is expressed also on non-hematopoietic cells, such as keratinocytes, primary sensory neurons, skin fibroblasts, synovial cells and chondrocytes [31,32,40–42]. The H_4R is proposed to be present also on cells of the central nervous system, the endocrine system and the kidney [43–47]. However, greatest caution should be exerted in interpreting these studies, since many data were obtained using antibodies whose specificity is strongly questioned [10,48]. Such antibodies, esp. those recognizing the H_4R, have been used also in studies examining the function of histamine or histamine receptors in the intestine. These studies were only included into this commentary when the histamine receptor expression was analyzed by at least one other independent technique, i.e. RT-PCR [49]. It, however, should be also kept in mind that the presence of mRNA for a given gene does not automatically imply the presence of a functionally active protein. Moreover, we strongly recommend generally avoiding the use of GPCR antibodies unless their specificity has been rigorously validated [50]. Moreover, often the purity of isolated cells is not documented, giving rise to the possibility that they have not been highly pure. Accordingly, a functional effect cannot be unambiguously assigned to a specific cell type.

1.5. Histamine in the intestinal inflammatory response

In addition to the well-described function of the mast cell as main producer of histamine in allergic inflammation [26], in the intestine of IBD patients increased numbers and activity of mast cells as well as elevated levels of histamine were detected [51–56]. Furthermore, expression of mRNA encoding H_1R, H_2R, and H_4R has been found in human intestinal tissue [49]. The involvement of histamine in IBD in humans is, therefore, very likely. In mouse models, the involvement of histamine in colitis is well documented. For example, the genetic deficiency of the histamine-generating enzyme HDC in mice ($HDC^{-/-}$ mice) leads to a protection against experimentally induced colitis [57]. Qualitatively, this protection is at best modest, probably due to the leakiness of the $HDC^{-/-}$ mouse model, in which residual amounts of histamine can still be detected [7,58]. Bene et al. [57] fed their mice with a histamine-free diet for 2 weeks before starting the experiment. Unfortunately, whether this indeed led to truly histamine-free mice was not reported. Despite this observation indicating a putative function of histamine in colitis, however, detailed information on such function of histamine, e.g. the receptor subtypes involved, in the inflammatory response in the gut is very sparse.

1.6. Pre-clinical animal models

The involvement of histamine in intestinal diseases has been analyzed in rats, mice and monkeys (Table 1). In the rat, the genetic deletion of functional *c-kit* expression leads to the deficiency of connective tissue-type and mucosal-type mast cells. In these *Ws*/*Ws* rats, symptoms of colitis, which was chemically induced by feeding dextran-sulfate sodium (DSS), and mucosal histamine concentrations were attenuated as compared to wild type controls [59]. Colitis symptoms affected were body weight gain, relative colon wet weight, and macroscopic colonic damage. Microscopically, however, mucosal damage, i.e. inflammatory infiltration, and crypt and epithelial loss, as well as myeloperoxidase (MPO) activities were comparable in both DSS-fed wild type and *Ws*/*Ws* mice. Thus, in this colitis model the deletion of *c-kit* does not seem to affect mucosal inflammation but rather edema formation and errosion. It has also to be taken into account, that the *Ws*/*Ws*