Histamine-2 Receptor Antagonists as Immunomodulators: New Therapeutic Views?

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Considerable evidence has emerged to suggest that histamine participates in the regulation of the inflammatory response, immune reaction, coagulation cascade, and cardiovascular function. Furthermore, histamine may play a major role in the growth of normal and malignant tissue as a regulator of proliferation and angiogenesis. Specific histamine receptors have been identified on the surface of bone marrow cells, immune competent cells, endothelial cells, fibroblasts, and also on malignant cells. This has prompted research in regulation by specific histamine receptor agonists and antagonists. Results from such studies are currently accumulating and suggest that the histamine-2 receptor antagonists have potential beneficial effects in the treatment of certain malignant, autoimmune and skin diseases, either alone or in combination with other drugs. The beneficial effect of histamine-2 receptor antagonists as adjuvant single drugs to reduce trauma-, blood transfusion- and sepsis-induced immunosuppression has led to research in combined treatment regimens in major surgery, particularly, of patients operated on for malignant diseases.

Key words: histamine; histamine receptor antagonists; surgery; malignant disease; autoimmunity; skin disease; HIV infection; leukaemia.

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Introduction

Histamine has been considered an effector molecule in chronic and immediate hypersensitivity responses (1, 2), but much evidence suggests that histamine is also a strong modulator of the immune system acting on specific histamine receptors expressed on immune competent cells (reviewed in (3, 4)). Histamine may act as an immunostimulant in physiological concentrations primarily via binding to histamine (H)-1 receptors (3), but also to a certain degree via binding to H-2 receptors (3, 5). Increased pathophysiological concentrations, however, may lead to immunosuppression via preferential binding to H-2 receptors (3, 6–8). Histamine may also bind to H-3 and intracellular (H_{IC}) receptors (9, 10), but the immune modulation induced by this binding is largely unknown. It is well known that histamine is released from mast cells and basophils immediately after traumatic events (11, 12), and that it may participate in mediation of the inflammatory response (13) and trauma-induced immunosuppression (4, 8, 12). This has intensified research in other potential actions of the molecule, and at present, histamine has been disclosed to have several additional physiological and pathophysiological actions apart from hypersensitivity mediation (Table 1).

Because histamine may be a potent mediator of immune competence in health and disease acting via

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Table 1. Additional roles of histamine.

Immunomodulation	(3, 5–8, 14–17)
Wound healing	(18–21)
Coagulation	(22, 23)
Cardiovascular regulation	(24, 25)
Neuroendocrine regulation	(26)
Endotoxic shock mediation	(27)
Peritoneal adhesion formation	(28)
Autoimmune disease	(29)
Growth of solid tumours	(20, 30–32)
Leukaemia	(33, 34)
HIV infection	(35, 36)

specific receptors (37, 38), H-1 and/or H-2 blockade was expected to modify the response, which could be of major interest in the treatment of certain immune-related diseases. Results from experimental studies suggest that H-1 blockers may inhibit the normal development of an immune response to antigen stimulation (3, 17, 39). Therefore, the potential of improving immune competence in disease has been attributed primarily to H-2 receptor antagonists (H-2RA) in the treatment of: (i) trauma-induced immunosuppression; (ii) solid tumours; (iii) leukaemia; (iv) psoriasis; and (v) miscellaneous disorders.

Trauma-induced Immunosuppression

Much evidence has emerged to demonstrate pronounced trauma-induced alterations in the immune system. While minor operations may stimulate immune reactions (4), major surgery and traumatic events inevitably induce immunosuppression, which may be related to trauma-induced histamine release (4, 11, 12). The consequences of reduced post-traumatic immune competence may be increased risk of infectious complications (4). Trauma and blood transfusion may be major determinants in development of trauma-induced immunosuppression (4, 40, 41), while anaesthesia may be of minor importance (42). Experimental studies have suggested a beneficial effect on reduction of immunosuppression by H-2RAs (4), which may be of potential benefit in trauma and major surgery. As histamine appears to be released immediately after a traumatic event (12), it was argued that H-2 blockade given before major surgery would be of optimal value (4). The effect of the H-2 blockers ranitidine or cimetidine in reducing trauma-induced immunosuppression after major, elective surgery have been confirmed by several human studies (4, 43–46), where the treatment was initiated before skin incision. Results from a human study of sepsis, however, have shown a potential immunomodulatory effect of ranitidine even after sepsis was diagnosed (47).

The clinical value of H-2RAs to reduce post-traumatic infectious complications is at present unknown, but clinical controlled, double-blind studies are being carried out in both elective and emergency colorectal surgery.

Solid Tumours

Patients admitted to surgery for solid tumours are frequently observed to have impaired immune competence (48, 49), which in part may be induced by the tumour cells (50–52). Whether impaired immune competence is detrimental to the host's defence against neoplastic formation, growth and dissemination is largely unknown. However, results from patients receiving blood transfusion (53), patients receiving immunosuppressive therapy after homologous transplants (54), or beneficial results from cancer patients treated with immunomodulatory substances without any direct effect on neoplastic cells (55) are the best available evidence that impaired immune competence may be detrimental for cancer patients (56). Preoperative immunosuppression in cancer patients may increase their risk of developing postoperative infectious complications (57). Trauma-induced immunosuppression may increase the risk of cancer recurrence at least in animals (58, 59). Theoretically, bone marrow micrometastases in humans (60, 61) may be stimulated and released into the circulation (62) by the surgical trauma. This may support the use of perioperative immunomodulation in major surgery for malignant disease (63).

Histamine levels appear to be enhanced (64) and its metabolism decreased (65) in patients with solid tumours. Primarily, enhanced histamine synthesis and release may have a beneficial effect in resistance to tumour establishment (66), but secondarily it may lead to immunosuppression, which subsequently may play a detrimental role in resistance to cancer growth and dissemination (32).

Reduced survival of patients with high amounts of mast cells in the inflammatory infiltrate of the growth border of their tumour (67) may underline the negative role of histamine in established neoplasia.

Experimental studies have shown H-1RAs to increase cancer cell growth (68), while H-2RAs may inhibit establishment, growth and dissemination (31, 68, 69) by immunomodulation or by direct blockade of H-2 receptors expressed by malignant cells (70). Among others, these results have argued for potential clinical effects in the treatment of cancer patients (71–73), and it has been shown that perioperative ranitidine may reduce suppression in specific immune parameters with major impact on cancer resistance (74–76). Single therapy with cimetidine has been shown to prolong survival in resectable gastric and colorectal cancer (77–79), and cimetidine and ranitidine prolonged survival in few patients with disseminated disease (80). Ranitidine improved immune response, tumour response and survival in few patients with liver metastases from colorectal cancer (81), indicating both immunomodulatory and direct actions of H-2RAs in neoplasia.

Results from large trials using cimetidine or ranitidine as adjuvant treatment in patients resected for gastric cancer, or primary and disseminated colorectal cancer are awaited with interest.

Leukaemia

Recently, it was suggested that histamine played a role in the immunopathogenesis of leukaemia (33, 34, 82). The potential role of H-2RAs has been studied in more chronic forms of leukaemic diseases, such as multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). Cimetidine improved natural killer (NK) cell function in patients with CLL (83), and ranitidine improved monocyte superoxide production, while

NK-cell function was reduced in patients with MM (84). CLL is a chronic disease with relatively good prognosis, if frequent and severe bacterial infections with pneumococcus pneumonia and/or *Haemophilus influenzae* can be treated (85). Prophylactically, the patients are offered vaccination against these two diseases every autumn, but the clinical effect seems to be poor. This may be based on decreased capacity to produce valid immunoglobulins (86). Based on our previous result of improvement of postoperative antibody synthesis to preoperative vaccination by ranitidine (75), we vaccinated CLL patients using simultaneous injection of pneumococcus pneumonia and tetanus toxoid. One half of the patients were given adjuvant treatment with ranitidine 300 mg twice daily for one month, and we showed ranitidine to improve synthesis of antitetanus antibodies significantly, while there was no effect on antipneumococcus antibody synthesis, which was absent in all patients (87). Adjuvant treatment with ranitidine, however, improved antibody synthesis to both tetanus and *Haemophilus influenzae* using the tetanus toxoid-conjugated *Haemophilus influenzae*-type B vaccine in a subsequent study of CLL patients (34). The high histamine concentration detected in these patients before vaccination was not changed by ranitidine treatment, indicating that ranitidine may primarily inhibit the action of histamine by blocking H-2 receptors (34).

Psoriasis

Psoriasis has been recognized as an autoimmune disease (88), in which histamine may play a role in the immunopathogenesis (89). The potential benefit of H-2RAs in this disease has been discussed in several small reports (89–92). Results from open studies on the effect of long-term systemic ranitidine (300 mg twice daily) comprising 20 patients each (93, 94) showed significant improvement in about two-thirds of the patients. Previous experiences with transient worsening of psoriasis in some patients (90), presumably by ranitidine-induced enhanced histamine release (29, 89), caused specific interest in that phenomenon (94). Therefore, the patients were instructed to report every detail of disease activity at the first outpatient visit after one month, and 13 of the 20 patients experienced initial mild to moderate worsening in the disease (94).

Eleven of those 13 patients subsequently experienced significant improvement of their disease. Both plasma and psoriatic skin microdialysate histamine concentrations were enhanced in patients compared to healthy volunteers and, as hypothesized (29, 89), histamine increased significantly in patients with worsening psoriasis and decreased towards normal levels during improvement in their condition (L. J. Pedersen et al., unpublished). A clinical, double-blind study is needed, however, to evaluate the benefit of the treatment. It is very uncommon, and may be ethically indefensible, for patients receiving treatment for a disease to experience worsening symptoms before they feel any benefit.

Normally, patients with worsening and severe side-effects are excluded from controlled studies, but this may be inappropriate when evaluating ranitidine in the treatment of psoriasis, because patients with worsening symptoms may be the ones who eventually benefit.

Miscellaneous Diseases

Theoretically, histamine may also participate in the pathogenesis of other diseases where impaired immune competence plays a role. This seems to be supported by beneficial reports of H-2RAs in HIV infection (95, 96), herpes zoster infection (97), periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis (the FAPA syndrome) (98), systemic mastocytosis (99), perennial allergic rhinitis (100) and subacute sclerosing panencephalitis (101).

Conclusion

Much evidence has emerged suggesting the value of H-2RA in certain immune-associated diseases, particularly in trauma-induced immunosuppression, solid tumours, leukaemia and psoriasis. At present, human dose–response studies of H-2RAs are not available, but so far normal antiulcer doses have been effective in the reduction of trauma-induced immunosuppression (4). In some studies of metastatic colorectal cancer (81), leukaemia (34, 87), psoriasis (93, 94) and HIV infection (96), however, oral ranitidine 300 mg twice daily has been proven effective and without obvious side-effects. Hypoacidity during long-term treatment with H-2RAs has been suggested to induce gastric and/or oesophageal malignancy, but this has not been supported by several epidemiological studies (102–104). Furthermore, H-2 blocker-induced hypoacidity has been assumed to have a detrimental role on gastric colonization, which may lead to pneumonia in critically ill trauma patients (105). This assumption was not supported by experimental trials (106) nor by large clinical trials (107–109). The suggestion that H-2RA-induced hypoacidity may not be a problem in promotion of neoplasia or pneumonia, even in critically ill patients, seems to be supported by the findings that gastric pH may be normalized within a few days despite continuous H-2 blocker treatment (110, 111). Finally, it has been suggested that the H-2RAs may have free radical scavenger effects (76, 112–114). This supports the assumption that the drugs may not have detrimental effects on neoplasia and gastric colonization (115, 116).

Although there seems to be a new therapeutic area for histamine-2 blockers, results from major clinical, placebo-controlled studies have to confirm or disprove the overwhelming amount of evidence from the above-mentioned studies before treatment outside clinical trials can be commonly recommended. Side-effects caused by H-2RAs are very rare, but normal precautions should be taken for the well-known central nervous system

reactions to rapid intravenous H-2 blocker administration (117).

Future Clinical Trials

Future clinical trials should be performed to clarify the dose–response relationship, as well as the effects of H-2RAs in combination with IL-2 or other recombinant cytokines (118, 119) and cytotoxic agents (120) should be considered. Reports of exciting new treatment potentials in the treatment of solid tumours have accumulated, such as gene therapy, vaccination therapy, cell-transfer therapy and induction of human leucocyte antigen (HLA) restriction antigens on neoplastic cells. At present, however, surgery is still the major option for most patients with solid tumours, and clinical experience suggests that immuno- and/or chemotherapy has its greatest impact when cell kinetics are optimal and the tumour burden optimally reduced. One option to keep an optimal immune competence despite major surgery may be adjuvant therapy with H-2 blockers alone or in combination with other biological response modifiers. Therefore, future clinical trials should consider the benefit of initiating adjuvant biological treatment before development of the trauma. Also, developments in the area of minimal surgical performance (121), reduced use of blood transfusion (41, 122), changed anaesthetic procedures and adequate pain relief (42) may have additional advantageous effects on clinical performance.

The practical use of new immunotherapeutic modalities would be much improved if those patients most likely to respond could be prospectively identified. Detailed knowledge is urgently needed; for example, of tumour–host local and systemic reactions. In research studies of cancer treatments, new regimens are primarily performed in end-stage patients with large tumour burdens. Obviously, this has the danger of yielding false-negative results for a regimen that might be active and beneficial in patients with resected or reduced tumour burdens. Clinical experience shows that far from all patients respond to a given treatment and, therefore, future treatment modalities ought to be more selectively based on objective criteria. In future, H-2 blockers may have a place in selective treatment modalities.

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