Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies

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Histamine

Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies

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There is altered expression of histamine H_1 and H_2 receptor subtypes in mucosal biopsies from the terminal ileum and large intestine of patients with symptoms of food allergy and/or irritable bowel syndrome

The research article by Sander and colleagues[1] in this issue of *Gut*, reports their results for expression of histamine receptor subtypes in the human intestinal tract from normal individuals and patients with symptoms of the irritable bowel syndrome (IBS) and/or food allergies ***(see page 498)***. Work of this nature was overdue because most of the available histological and functional data for histamine receptors in the small and large intestine were obtained from animal models. The authors' principal findings for the human bowel are in general agreement with the animal literature that reports on expression of the histamine H_1, H_2, and H_4 receptor subtypes in the enteric nervous system (ENS), intestinal musculature, mucosal epithelium, and immune/inflammatory cells. In contrast, the finding by Sander and colleagues[1] that histamine H_3 receptors are not expressed in the human bowel was unexpected in view of the clearcut evidence for functional involvement of the H_3 receptor subtype in the nervous control of motility, secretion, and blood flow in guinea pig intestine, which serves as the primary animal model.[2–5]

The authors' evidence for altered expression of histamine H_1 and H_2 receptor subtypes in mucosal biopsies from the terminal ileum and large intestine of patients with symptoms of food allergy and/or IBS is consistent with current concepts for the involvement of histamine release from enteric mast cells and its paracrine signalling function in the ENS as an underlying factor in these two disorders.[5–8] Histamine is not expressed by enteric neurones and is not a neurotransmitter in the ENS.[9] Its signalling function is paracrine in nature through release from enteric mast cells and inflammatory granulocytes. Mastocytosis and presumably elevated availability of histamine are present in microscopic colitis, parasitic infections, IBS, and no doubt additional functional gastrointestinal disorders associated with symptoms of cramping abdominal pain, watery diarrhoea, and defecation urgency.[6 8 10–17]

The appearance of histamine H_2 receptors in human myenteric ganglia is reminiscent of expression of the H_2 receptor subtype in the guinea pig ENS. Binding of histamine to H_2 receptors on enteric neuronal cell bodies in the guinea pig, either during exogenous application of histamine or by degranulation of neighbouring mast cells, elevates neuronal excitability characterised by firing of longlasting trains of nerve impulses.[18–21] In the case of submucosal secretomotor neurones, elevated firing rates increase the volume of mucosal secretions of electrolytes and H_2O and thereby increase the liquidity of the intestinal contents, which in turn can underlie neurogenic secretory diarrhoea.[22] For musculomotor neurones in the myenteric plexus, histamine H_2 evoked firing alters contractile behaviour of the muscularis externa that is coordinated with organised secretory patterns.[23 24] Similar outcomes for

release of histamine and its actions at the H_2 neuronal receptors, now reported by Sander and colleagues[1] for human ENS, can be reasonably assumed. Nevertheless, progress in understanding specific pathophysiological malfunctions and therapeutic improvisation requires that future human research be pursued along the lines of what has been done in basic science models.

Excitation of ENS neuronal perikarya is one of the significant actions of histamine at the H_2 receptor subtype. A second important action, which has been well documented in the guinea pig enteric ENS but not in humans, is suppression of synaptic transmission.[2 19 25] Exposure of the ENS to histamine, either by exogenous application in vitro or by release from sensitised mast cells in response to allergins (for example, food proteins or infectious organisms), suppresses neurotransmitter release at four important information transmission nodes in the neural microcircuitry. Which are: (1) fast excitatory nicotinic synapses; (2) slow excitatory synapses where serotonin, substance P, calcitonin gene related peptide, and ATP are among the putative neurotransmitters; (3) slow inhibitory synapses, especially on submucosal secretomotor neurones, where norepinephrine release from the sympathetic innervation and somatostatin released from intrinsic neurons are inhibitory neurotransmitters; and (4) sympathetic neurovascular junctions.

Inhibition of neurotransmission in each of these cases is presynaptic. Stimulation of presynaptic inhibitory receptors by histamine suppresses the release of neurotransmitter from the presynaptic axonal terminal and thereby inhibits transmission of neural signals. Inhibition of transmission at the multitude of nicotinic synapses in the enteric neural networks would be expected to prevent ''call-up'' of selective behavioural programmes or to selectively activate a specific programme in the ENS library of programmes (for example, intestinal defence).[5] Suppression of slow excitatory transmission, either at selective slow synapses or in combination with suppression of fast nicotinic transmission, is probably also involved in generation of the pattern of defensive intestinal behaviour, which can be demonstrated during exposure to sensitising antigens in previously sensitised animals. Slow inhibitory postsynaptic potentials (IPSPs) in submucosal secretomotor neurones impose a braking action on neurogenic secretion that is removed when histamine is applied experimentally or released from enteric mast cells in sensitised animals. Removal of the sympathetic brake from secretomotor neurones is a factor underlying the diarrhoeal states associated with allergic responses and mucosal inflammation.[2] Suppression of norepinephrine release at submucosal neurovascular junctions removes the sympathetic braking action on blood flow, which in effect supports stimulation of neurogenic mucosal secretion.[4]

Several types of presynaptic inhibitory receptors are expressed in the ENS, one of which is a histaminergic receptor. The presynaptic histaminergic inhibitory receptor in the guinea pig ENS belongs to the histamine H_3 receptor subtype. The slow IPSPs in guinea pig secretomotor neurones, which are mediated by release of norepinephrine and somatostatin, are suppressed by histamine.[2] Selective histamine H_3 agonists, but not histamine H_1 or H_2 agonists, act presynaptically to suppress IPSPs, and selective H_3 antagonists, but not H_1 or H_2 antagonists, block both the effects of exogenously applied histamine and the effects of histamine released from mast cells in sensitised animal preparations.[2 19–21 25] Likewise, suppression of excitatory neurotransmission at other neural synapses and neurovascular junctions reflects histamine H_3 mediated inhibition of neurotransmitter release.[4]

Absence of the histamine H_3 receptor subtype from human bowel, as reported by Sander and colleagues,[1] was unexpected and is paradoxical in view of the evidence in the literature for its expression and importance in the animal model. Data to explain the paradox are not readily available. On the one hand, failure to find the human receptor with any of three valid methods (that is, immunohistochemistry, western blot, or reverse transcription-polymerase chain reaction) strongly supports the conclusion that the H_3 receptor is not expressed in human bowel. On the other hand, evidence from physiological studies convincingly supports expression and important functional significance of the receptor in the guinea pig model. This is a dilemma raised by Sander and colleagues.[1]

The importance of histamine release from enteric mast cells in terms of intestinal symptoms, which are associated with human allergy, IBS and brain-gut interactions in stress is widely supported and convincing.[12–15 26] Symptoms of watery diarrhoea, urgency, cramping abdominal pain, and intestinal hypersensitivity to distension in humans appear in general to have a counterpart in animal models, whether it is a guinea pig, rat, or canine model.[5 6] These symptoms are perceived as side effects of the ''running'' of a specific ENS neural programme that has evolved as a defensive mechanism for rapid expulsion from the intestine of a threat to the integrity of the whole animal. If this is indeed the case, then the mechanisms of histaminergic call-up of programmed intestinal defence are not expected to differ much across mammalian species. Most of the results reported by Sander and colleagues[1] are consistent with this concept, except for the absence of the histamine H_3 receptor subtype. Histaminergic presynaptic inhibition that removes the sympathetic brake on secretion and mucosal blood flow would seem to be a necessary requirement in the ''running'' of the secretory component of the neural defence programme that ''flushes'' threatening agents and organisms from the mucosa and maintains them in suspension in a fluid filled intestine awaiting clearance by powerful propulsive motility.

In view of the importance of immune/inflammatory cells and histamine signalling in the ENS, thorough understanding for the human gut is imperative. A credible start in this direction has been made by Sander and colleagues.[1] Now, neurogastroenterological research must determine whether presynaptic inhibition in the ENS has the same significance for the common symptoms of food allergy, mucosal inflammation, and brain-gut interactions in stress in humans, as is known to exist in animal models. If this proves to be the case, then additional investigation will be needed to determine if it might be mediated by a histamine receptor other than the H_3 subtype.

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Crohn's disease

Crohn's disease: why the disparity in mortality?

E V Loftus Jr

There has been no significant decrease in mortality in patients with Crohn's disease over the last several decades

It is well accepted that Crohn's disease is associated with a small but real risk of death. Population based reports from Sweden,[1 2] Denmark,[3] and Italy[4] indicate that Crohn's disease patients have a higher mortality rate than expected, although at least one notable exception from the UK demonstrated survival similar to the general population (table 1).[5] A preliminary report from Olmsted County, Minnesota, indicated a mortality rate that was about 20% higher (but not significantly different statistically) than that expected,[6] standing in contrast with the results of a previous report from the same location.[7] The largest study of mortality in Crohn's disease was from a cohort of approximately 6000 patients identified through the General Practice Research Database (GPRD), which contains the computerised medical records of 6% of the British population.[8] The annual mortality rate in Crohn's disease was 1.6% compared with 1.0% in age, sex, and practice matched controls. After adjusting for age, sex, and cigarette smoking, it appeared that the risk of death was 73% higher in Crohn's disease patients than in controls.[8] Although the large cohort size makes this study important, its generalisability is limited by the fact that the cohort was a mixture of incidence and prevalence cases, the average age at entry into the cohort was 42 years (higher than the average age at diagnosis of Crohn's disease of late 20s/early 30s in most studies), and the average follow up was only three years. A recent systematic review of "hard end points" in population based cohorts of Crohn's disease concluded that there was no evidence for a significant change in disease outcome over the past 40 years.[9] To summarise, these studies suggest that the mortality rate in Crohn's disease ranges from 30% lower than expected to 70% higher than expected. All of these studies are limited by the fact that most of the patients in these cohorts were not only identified retrospectively, but also diagnosed before the "modern era" of medical therapy for Crohn's disease.

The European Collaborative Study Group of Inflammatory Bowel Disease (EC-IBD) prospectively developed a cohort of patients newly diagnosed with Crohn's disease and ulcerative colitis at 20 European and Israeli centres between October 1991 and September 1993. The incidence of Crohn's disease at these centres over this two year period[10] and the clinical course in these patients in the first year after diagnosis[11] have been previously reported. In the present issue of *Gut*, Wolters and colleagues[12] update the follow up of approximately half of the original EC-IBD cohort of Crohn's disease patients (n = 371) to determine absolute, relative, and cause specific mortality ***(see page 510)***. Median age at diagnosis of Crohn's disease was 31 years (range 15–83). Follow up was complete in 92% of the cohort. After an average follow up of approximately 10 years, 37 patients had died (10%). Expected rates of death were calculated using country, age, and sex specific rates from the World Health Organisation (WHO) mortality database. Using actuarial techniques, the 10 year risk of death was 10% versus 7% expected. One would have expected 21 patients to have died based on the WHO mortality rates. The standardised mortality ratio (SMR, which can be thought of as a relative mortality rate) was 1.85, or 85% higher than expected.

The authors examined their cohort for risk factors. For both sexes, SMR was significantly higher than expected.[12] The relative risk of death was numerically higher in the northern European centres (SMR 2.0 (95% confidence interval (CI) 1.3–3.0)) than in southern ones (SMR 1.6 (95% CI 0.8–2.7)) but this difference was not statistically significant. When the SMR analysis was stratified by various aspects of the phenotypic Vienna classification,[13] age ⩾40 years at diagnosis (SMR 1.99 (95% CI, 1.4–2.8)), colonic involvement at diagnosis (SMR 2.1 (95% CI 1.3–3.1)), and inflammatory disease behaviour at diagnosis (SMR 2.2 (95% CI, 1.5–3.2)) all appeared to be associated with increased mortality risk. However, in a multivariate