Easy as 1, 2, 3? Histamine receptors and gastric acid

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N-alpha-methyl-histamine, which is produced in the gastric mucosa by Helicobacter pylori, is a potent H$_1$ receptor agonist as well as a H$_3$ receptor agonist

It is over 80 years since the stimulatory effect of histamine on gastric acid was reported. The observation that the conventional antihistamines (subsequently shown to be H$_1$ antagonists) failed to block the acid stimulatory action ultimately led to the discovery and availability of H$_2$ antagonists. These were not only effective drugs but tools to dissect acid secretory physiology, and develop our continually evolving paradigm of histamine as the major paracrine stimulant of gastric acid.

In the gastric mucosa, histamine is found within enterochromaffin-like (ECL) cells and mast cells, the relative proportion of the two cell types being species and site dependent. Histamine is formed by the decarboxylation of histamine by histidine decarboxylase (HDC). After release histamine is enzymatically deactivated by two pathways. The majority is methylated onto one of the nitrogen atoms in the imidazole ring by imidazole-N-methyltransferase, and a smaller proportion is degraded by oxidative deamination to imidazole acetic acid. A further potential methylation site is on the terminal nitrogen of the side chain, producing N-alpha-methyl-histamine (NAMH). In 1935, soon after it was first chemically synthesised, NAMH was shown to be a potent stimulant of canine acid secretion. NAMH was detected in canine gastric juice following histamine stimulation, and was more than twice as potent as histamine in stimulating acid secretion. The acid stimulatory action was sensitive to H$_2$ blockers. Although a broad specificity mammalian enzyme capable of catalysing side chain as well as ring methyla-

The recent description of a fourth receptor type$^{22}$ emphasises the fact that we still have much to learn about the
Cancer

UGT1A1 polymorphisms and colorectal cancer susceptibility

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UDP-glucuronosyltransferase (UGT) 1A7 polymorphisms may be involved in the aetiology of colorectal cancer

The contribution of the xenobiotic metabolising enzymes (XMEs) to disease susceptibility, particularly cancer, has been a focus for a great deal of research over the last two decades. Many of these genes are polymorphic and exhibit significant interindividual variation in their activity. Although these enzymes all have endogenous substrates, they are also involved in the metabolism of exogenous, often mutagenic, substances to which humans are exposed. The central hypothesis of these studies has been that genetic changes functionally alter the enzymes and consequently modify an individual’s response to a given exposure, putatively associated with the disease. The increased risk for the individual is likely to be small. However, the higher frequency of these alterations, compared with the risks associated with genetic defects implicated in familial syndromes, raises the possibility that the attributable risk, at the population level, may be substantial and therefore of considerable public health importance.

The involvement of UDP-glucuronosyltransferase (UGT) 1A7 polymorphisms in the aetiology of colorectal cancer (CRC) is presented by Strassburg et al in this issue of Gut [see page 851] is biologically plausible. The authors have shown that UGT1A7 contributes to the elimination of substances to which humans are commonly exposed and many of these substances are known to be mutagenic. The polymorphism is relatively common and has been demonstrated to affect enzyme function. Also, expression of this gene has been detected in the colon. However, these factors are true for other gene variants for which only weak and inconsistent associations have been observed.

Strassburg et al report about a twofold increase in the risk of developing CRC for those possessing the UGT1A7*3/*1 and UGT1A7*3/*2 genotypes (odds ratio (OR) 2.26 (95% confidence interval (CI) 1.09–4.68) and OR 2.39 (95% CI 1.15–4.99), respectively) and an almost threefold increased risk associated with the presence of the UGT1A7*3 allele (OR 2.75 (95% CI 1.6–4.71)). There are a number of factors that should be considered when interpreting studies of this type.

A case control study relies upon the comparison between subjects with a given disease and those unaffected; it is therefore crucially important that the case and control subjects are representative of the population with the disease and at risk of the disease, respectively. The response rates for both case and control groups should be stated and it is important to consider whether cases are newly incident, otherwise there may be a bias associated with selection; if possible, archived records should be consulted to determine if the case group is typical.

The control subjects used by Strassburg et al were “healthy blood donors”; although blood donors are a commonly used source of control subjects, they are not necessarily a representative sample of the population at risk of colorectal cancer. Ideally, control subjects should be recruited from the population from
Liver disease

HCC: What’s the score
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Choosing a scoring system for staging hepatocellular carcinoma is a difficult task

Primary hepatocellular carcinoma (HCC) is a common neoplasm in East Asia, Africa, and the Mediterranean countries, with an age adjusted incidence rate of up to 20–28 cases per 10^5 in men. Major progress has been made in the prevention of HCC through universal vaccination of neonates and children at risk worldwide, yet available treatment options for patients with established tumours rarely lead to complete cure. HCC is recognised for its heterogeneous clinical and biological presentation, variable natural course, and its relationship to defined risk factors and aetiologic agents, as well as the difficulty in predicting response to different modes of treatment. The time interval from an undetectable tumour to a 2 cm lesion may vary between four and 12 months which leaves a relatively narrow window for optimal intervention in already established tumours with a fast doubling time. In the past decade, a number of new palliative and potentially curative means of treatment have been introduced in the clinical management of HCC. However, evaluation of efficacy of interventions such as surgical resection, ablative procedures including alcohol injection, chemoembolisation, radiofrequency, and liver transplantation is difficult without agreement on universal surveillance and staging systems for early identification and follow up of HCC.
Randomised controlled trials for assessment of surveillance and intervention become exceedingly difficult to perform in the presence of a plethora of new treatment modalities, frequently of unproven efficacy. The need for a universal tool for allocation of patients into defined groups within clinical trials and assessment of success of treatment has recently been addressed by a number of groups in Western Europe and Japan.\textsuperscript{10} There is no argument about the fact that prolonged survival with an acceptable quality of life is the desired end point for any mode of intervention. However, there is less agreement on which tools to employ for optimal selection of therapeutic modes dictated by the clinical needs of defined stages of the disease.

Initially, the Child-Pugh scoring system was used for identification of HCC candidates for therapy.\textsuperscript{9} However, the Child-Pugh classification only addresses the functional capacity of the liver without including any tumour parameters. In contrast, the TNM (tumour node metastasis) classification or its variant pTNM uses only tumour related parameters (three aspects of the functional capacities of the liver) for identification and follow up of HCC candidates for treatment. The TNM staging system, although often used by surgeons for assessment of success of surgical resection and liver transplantation, has been criticised for lack of prognostic value and has been virtually abandoned.\textsuperscript{10}

Twenty two years after introducing the Child-Pugh scoring system, Kunio Okuda suggested a new staging system which provides a tool for combined assessment of liver function and tumour load.\textsuperscript{3} It includes three stages depending on tumour size (more or less than 50% of the liver area affected) and the functional capacity of the liver, as assessed by albumin and bilirubin levels and the presence of ascites. Yet the new staging system still requires some modifications as it lacks a means of assessment of vascular invasion or “geographic” tumour distribution within the liver lobes and is not predictive enough for small tumours. New parameters such as the presence of portal vein thrombosis, unifocal or multifocal tumours, elevated alkaline phosphatase and AFP levels, and performance status have been proposed for inclusion in staging systems for HCC patients.\textsuperscript{5} Since 1998, three new scoring systems have been proposed by European groups for evaluation of HCC candidates for treatment, namely the CLIP score\textsuperscript{3} (Italian investigators for cancer of the liver program), the BCLC score\textsuperscript{6} (Barcelona clinic liver cancer staging), and the French prognostic classification for predicting survival in HCC patients.\textsuperscript{7} The BCLC group introduced clinically relevant portal hypertension as a new prognostic parameter for HCC staging while the French scoring system includes elevated alkaline phosphatase and AFP levels (also used in the CLIP score) among the factors for evaluation of prognosis. All three new classifications include vascular invasion as an important prognostic tool.

In this issue of Gut, Levy and colleagues\textsuperscript{1} have compared the CLIP and Okuda classifications in a cohort of 257 Canadian patients [see page 881]. The seven grade CLIP scoring system combines the Child-Pugh stage (A, B, or C) with tumour morphology (unifocal or multifocal with <50% extension), AFP levels (<400 or >400 ng/ml), and the presence or absence of portal vein thrombosis as evidence of macro vascular invasion. In their study, the Toronto group clearly showed that the CLIP stage 0 score defined more accurately HCC patients with a good prognosis (67% with a five year survival) compared with the Okuda stage I score (identifying only 35% of patients with a five year survival). Furthermore, the CLIP classification was also superior in identifying HCC patients with a poor prognosis over a median survival time of 22.8 months. The report by Levi et al\textsuperscript{1} is a welcome contribution which confirms the original findings of the CLIP group reported in Italian patients. It therefore provides further validation of this classification, which has now been demonstrated in Canadian patients, half of whom were of East Asian origin. It also provides a comparison of the CLIP scoring with the Okuda and Child-Pugh systems, thus improving the prognostic tools available today for assessment of the treatment modalities for HCC. Further evidence as to the advantage of the CLIP classification has recently been reported from Japan.\textsuperscript{7} This retrospective evaluation comparing the CLIP, Okuda, and TNM classifications in 662 HCC patients confirmed the discriminatory ability and predictive power of the CLIP score over the Okuda and TNM scores in an East Asian population. Yet caution is advised before the optimal scoring method for staging of HCC can be recommended. The present study by Levy et al and the study from Japan\textsuperscript{7} are retrospective and prospective comparative evaluations and are very much needed. Recently, the European Association for the Study of the Liver (EASL) held a single topic conference on the clinical management of HCC.\textsuperscript{8} The report of this meeting of experts provides a comprehensive overview on the current state of available tools for surveillance, diagnosis, evaluation, and treatment of HCC. The final report of the Barcelona meeting acknowledges the pivotal factors affecting the prognosis of HCC, including: stage, aggressiveness, and growth rate of the tumour; the general health status of the patient and his liver function; as well as the selected intervention.\textsuperscript{9} However, no endorsement was given to a single staging system for HCC although a proposal was made for developing a prognostic model for the individual stages.

It is my opinion that the time is ripe for initiation of a multicentre prospective clinical evaluation of all 5–6 available scoring systems for HCC. Despite the complexity of such an effort, a well designed study with adequate representation of the various ethnic and geographic variables should be undertaken. The results would provide an answer as to which system is preferred for selecting the optimal (available or new) treatment(s) for patients at various stages of HCC and would contribute to validation of one or more of the scoring systems in question.

Gut 2002;50:749–750

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REFERENCES