Aspirin injury and *H. pylori*

A Schmassmann

The role of *Helicobacter pylori* in aspirin induced gastric injury

*Helicobacter pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) cause the vast majority of peptic ulcers and their complications. However, their interaction remains extremely controversial. The study of Yoshida et al in this issue of *Gut* aimed to address this issue by investigating the influence of experimental *H. pylori* infection on gastric mucosal injury induced by aspirin in male Mongolian gerbils [see page 594].

The study found that aspirin caused more extensive haemorrhagic erosions associated with greater myeloperoxidase activity (an index of neutrophil accumulation), thiobarbituric acid reactive substance concentrations (an index of lipid peroxidation), and KC/GRO concentrations (a chemoattractive cytokine in rodents) in infected than in uninfected gerbils.

Furthermore, the authors repeated the experiments in gerbils pretreated with antineutrophil serum which reduced circulating neutrophils by 77%. Erosion index, myeloperoxidase activity, and thiobarbituric acid reactive substance concentration (but not KC/GRO concentration) were significantly less in such neutrophil depleted gerbils exposed to *H. pylori* plus aspirin than in similarly exposed animals treated with control serum. Inhibitory effects on mucosal damage by antineutrophil serum administration was much greater in *H. pylori* infected gerbils (65%) than in uninfected gerbils (31%). Yoshida et al concluded that *H. pylori* infection potentiates aspirin induced gastric mucosal injury by mechanisms that include accumulation of activated neutrophils.

This is one of the first experimental studies showing convincingly that aspirin induced gastric injury is aggravated by *H. pylori* infection. Furthermore, Yoshida et al give strong support that *H. pylori* potentiates aspirin injury via a neutrophil dependent process. However, the study should be completed by proving that *H. pylori* eradication will reverse the severity of aspirin induced gastric injury to levels found in uninfected gerbils. The data of Yoshida and colleagues are well in line with recent experimental studies which have indicated that neutrophil adherence to the endothelium via various adhesion molecules is involved in the development of gastric mucosal injury induced by *H. pylori* infection or NSAID use. Activated neutrophils have been suggested to injure endothelial and epithelial cells by producing active oxygen species and proteases. These data suggest that *H. pylori* and NSAIDs can cause an acute inflammatory response in the gastric mucosa leading to neutrophil mediated injury. Yoshida and colleagues performed their studies in Mongolian gerbils infected with *H. pylori*. These infected animals develop pathological changes in the stomach that mimic those seen in humans infected by *H. pylori*. About three weeks after *H. pylori* inoculation, gerbils exhibit typical gastritis with neutrophil and mononuclear cell infiltration in the lamina propria. The gerbils subsequently show chronic gastritis (including formation of lymphoid follicles) approximately six weeks after *H. pylori* infection and develop gastric ulcers at more than six months after infection. This Mongolian gerbil model may allow, in additional studies, assessment of the role of *H. pylori* on NSAID induced ulcer development. It would be particularly interesting to assess the role of *H. pylori* eradication in gerbils six months after infection before experimental long term treatment with NSAIDs.

What to do about *H. pylori* in NSAID users who are infected with the organism poses a difficult therapeutic dilemma, which continues to be controversial. Whether *H. pylori* infection affects the outcome of NSAID therapy in humans is only partly clear at the present time. *H. pylori* gastritis seems to increase the likelihood of developing dyspeptic symptoms in patients on NSAID therapy. In addition, there is evidence that the histological severity of *H. pylori* gastritis may be adversely affected by NSAID therapy, with a consequent increase in the risk of developing a peptic ulcer, possibly with complications. Furthermore, ulcers are more likely to develop during the course of NSAID therapy in those infected with *H. pylori*; eradication of the infection reduces ulcer recurrence in the face of continued NSAID therapy, and it seems likely that this must reduce the risk of gastrointestinal bleeding in those using NSAIDs. The effect of *H. pylori* infection on the risk of perforation during NSAID therapy is unclear at the present time.

The mechanisms of NSAID injury to the gastrointestinal tract are complex and not mediated solely by activated neutrophils; several other mechanisms may be involved such as inhibition of prostaglandin and thromboxane synthesis, damage to blood vessels, inhibition of repair mechanisms, increase in gastrointestinal permeability, drug entrapment in gastric cells, uncoupling of oxidative phosphorylation in mitochondria, loss of cytoskeletal control over tight junction, decrease in gel hydrophobicity, inhibition of phospholipase, and interaction with inducible nitric oxide synthase and nitric oxide. In contrast, the effects of *H. pylori* on the gastrointestinal tract differ substantially from those NSAID related mechanisms. In particular, NSAIDs and *H. pylori* have opposite effects on prostaglandin synthesis; NSAIDs decrease whereas *H. pylori* increases prostaglandin synthesis in the gastric mucosa. The modest stimulatory effects of *H. pylori* on prostaglandin (and nitric oxide) synthesis are unlikely to confer significant protection in the presence of NSAIDs as *H. pylori* also produces a broad spectrum of pathophysiological changes—for example, reduction of viscosity of mucus, facilitating back diffusion of hydrogen ions and reduction of mucosal blood flow which have the potential to diminish the resistance of the gastric mucosa to NSAID exposure. Additionally, gastric acid secretion, which is increased in the majority of *H. pylori* infected subjects, favours gastric mucosal damage as the severity of NSAID damage is dependent on gastric pH.

In the future, it is possible that the impact of the questions mentioned above will decline because of the decreasing prevalence of *H. pylori* infection in the developed world and the increasing use of cyclooxygenase 2 inhibitors and new specific inhibitors of thromboxane aggregation (such as clopidogrel) which neither appear to cause ulcers nor to interact significantly with *H. pylori*.


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Pancreatitis

The SPINK in chronic pancreatitis: similar finds, different minds

H Witt

SPINK mutations are strongly associated with chronic pancreatitis but may not cause the disease

Student

“Yet in each word some concept there must be.”

“Quite true! But don’t torment yourself too anxiously;
For at the point where concepts fail,
At the right time a word is thrust in there.
With words we fitly can our foes assail,
With words a system we prepare,
Words we quite fittingly can believe,
Nor from a word a mere iota thieve.”

Johann Wolfgang Goethe; Faust I

In this issue of Gut, Threadgold and coworkers and Drenth and colleagues describe mutational studies of SPINK1 in two large series with different types of chronic pancreatitis [see pages 675 and 682]. Threadgold et al found the SPINK1 N34S mutation in 4/108 (3.7%) patients with hereditary CP in 6/7 (86%) cases of so-called “familial idiopathic CP”, in 11/87 (13%) patients with so-called “true idiopathic CP”, and in 4/67 (6%) patients with alcohol related CP. Drenth et al detected an N34S mutation in 2/10 (20%) patients with hereditary CP in 5/24 (21%) patients with idiopathic CP in 4/72 (5.6%) cases with alcohol induced CP and in 2/29 (22%) patients with a miscellaneous origin of CP.

Both studies showed a strong association between N34S and various types of CP but the mutation frequencies reported in different CP groups and the interpretation of their data differ markedly. In hereditary CP patients, Drenth et al found the N34S mutation in 20% whereas Threadgold et al detected this mutation in only 3.9%. Previous studies showed an N34S frequency in hereditary CP patients of 9.1% and 7.0%. These considerable differences may be partially explained by the fact that in some studies the N34S frequency was calculated by counting several members of one family whereas in other studies the frequency was determined by counting unrelated patients only. Furthermore, each group used different definitions of hereditary and idiopathic CP. Drenth et al diagnosed hereditary CP on the basis of two or more affected family members whereas Threadgold et al made the diagnosis of hereditary CP on the basis of two affected first degree or three or more affected second degree relatives in two or more generations. Thus in the latter study several patients with a family history where classified as having “familial” idiopathic CP. The concept of “familial” and “true” idiopathic CP appears strange as the term idiopathic usually implies the absence of any predisposing factor, including heredity. The chosen contradiiction in adjecto “familial idiopathic” throws light on different understandings of hereditary CP and reflects the lack of a uniform terminology. As the first description of inherited pancreatitis suggested an autosomal dominant inheritance, hereditary CP was defined as a dominant inherited disease. Subsequently, the finding of familial clustering in one generation only, which indicates other inheritance patterns such as recessive or complex trait, was blinded out in the disease concept of hereditary CP.

The observed N34S frequencies in alcohol related CP were similar in both studies published in this issue of Gut (6.0% and 5.6%, respectively) and are in line with the previously reported frequency of 5.8%. In contrast with Drenth et al however, Threadgold et al failed to find a significant association between N34S and alcoholic CP due to the high N34S frequency in their control subjects from the Liverpool area (4/100).

Interestingly, Drenth et al also found SPINK1 mutations in individuals in which the cause of CP was attributed to metabolic disorders or anatomical...
heterozygous for C282Y or bear no
matic haemochromatosis are only
clinical apparent liver disease. Moreover,
homozygotes however do not suffer from
(C282Y) in the
tyrosine substitution at position 282
caused in most cases by a cysteine to
ample, hereditary haemochromatosis is
mendelian inheritance patterns: for ex-
a more complex trait and not only simple
homozygotes, refusing a recessive trait does not
frequency of observed N34S heterozy-
ance pattern does not explain the high
expected. Although a recessive inherit-
ance patterns. For example,
different genes may have different inher-
tances in haemochromatosis families. Fur-
thermore, recent research showed that
haemochromatosis may also follow an
autosomal dominant trait caused by fer-
roportin mutations. In summary, haemo-
chromatosis may be induced by different
recessive, dominant, and complex
mechanisms in different genes. The
same is clearly true for CP. One may dis-
cover even if the terms dominant or recessive
are appropriate for these diseases, how-
ever they may be helpful to navigate
through the genetic sea, keeping in mind
that all models are only coordinate
systems but never image exactly the
reality.

Discussion of the role of SPINK1 in CP
(disease inducer, per se, modifier) re-
fects the lack of sufficient knowledge of
these as yet unidentified factors and
does not contribute usefully to the
understanding of inherited CP. Usually,
first is to identify the disease
causing gene or genes and later to isolate
modifying genes. Different mutations in
different genes may have different inher-
ance patterns. For example, PRSS1
mutations are thought to be dominant.
However, the PRSS1 A16V mutation is
mainly found in idiopathic CP

As the majority of patients with
idiopathic or hereditary CP do not show a
SPINK1 or PRSS1 mutation, several
other genes may be involved in the
disease pathogenesis. Future research
will identify more pancreatitis related
genes and will also more precisely deter-
mine the meaning of mutations in the
cystic fibrosis transmembrane conducti-
ance regulator (CFTR) gene in CP. Several
studies found a CFTR mutation in up to 30% of
patients with idiopathic CP. In contrast to Threadgold et al who
proposed that CFTR is not a good candi-
date gene for the second gene in patients with
SPINK1 mutations, we assume consistent with the opinion of Drenth et
al, that CFTR mutations have a major
impact on the disease pathogenesis.
Possibly, in a more sophisticated way, three or
more different genetic defects lead to CP. Future genetic studies on CFTR and other
candidate genes will give important
insights into the mechanisms of
inherited pancreatitis and will probably
lead to a complex genetic model.

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