Digest

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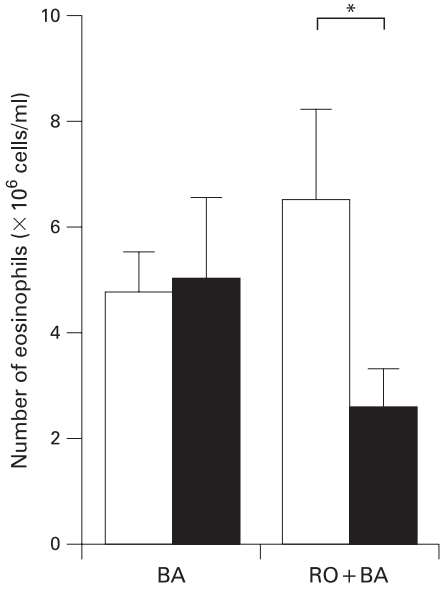
Significant interactions between reflux oesophagitis and bronchial asthma demonstrated in a novel rat model

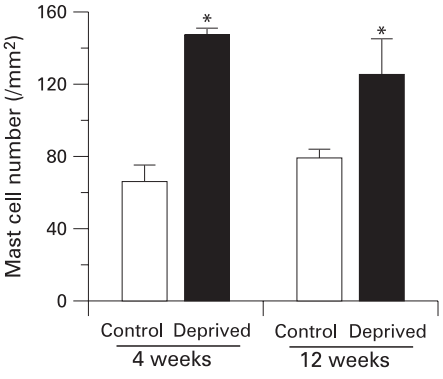
A strong association between reflux oesophagitis (RO) and bronchial asthma (BA) is widely appreciated. However, the mechanisms involved in this interaction are uncertain, partly due to the lack of suitable animal models. Sugawa and coauthors present a novel rat model to explore these interactions. RO and BA were induced in rats and these were divided into four groups: control, RO, BA and RO+BA. Inflammatory responses in the airways and in the oesophagus were determined. In bronchoalveolar lavage fluid increased number of cells, especially eosinophils, as well as higher levels of interleukin 13 were seen in the RO+BA group compared with the BA group and this enhanced airway inflammation was prevented by rabeprazole treatment (see fig). Moreover, eosinophilic infiltration in the oesophageal submucosa and levels of mRNA expression of several cytokines were enhanced in the RO+BA versus RO group. This novel rat model, demonstrating significant interactions between RO and BA, will most certainly be useful in further studies examining the association between these two diseases. ***See page 575***



Rabeprazole treatment reduced acid-induced increase in eosinophil counts in bronchoalveolar lavage fluid of rats with reflux oesophagitis (RO) and bronchial asthma (BA). White bars represent vehicle-treated rats and black bars represent rabeprazole-treated rats.

Neonatal stress leads to closer nerve–mast cell interaction

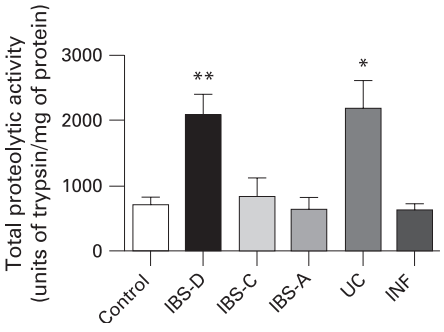
Increased numbers of mast cells have recently been described in the colonic mucosa of patients with irritable bowel syndrome (IBS). It is known that mast cells can be stimulated by stress, which is thought to be important in IBS. Rats deprived of maternal attention in the neonatal period display a number of abnormalities suggesting increased anxiety and neurotic behaviour. They are also known to exhibit hypersensitivity to colorectal distension, a feature seen in many patients with IBS. The study by Barreau and coworkers observed colonic but not jejunal mast cell hyperplasia and activation in maternally deprived rats 4 and 12 weeks after birth (see fig). The number of mast cells in close proximity to afferent nerve fibres was also increased, mimicking a phenomenon observed in patients with IBS. Synaptogenesis was demonstrated to be stimulated, a phenomenon which was abolished by treatment with anti-nerve growth factor antibodies. This suggests that neonatal stress acts through nerve growth factor to stimulate the growth of nerves in close proximity to mast cells, which may contribute to visceral hypersensitivity. ***See page 582***



Neonatal maternally deprived rats showed increased colonic mast cell numbers at both 4 and 12 weeks of age. *p<0.05 vs control.

Increased proteases in the stool of patients with irritable bowel syndrome with diarrhoea but not with constipation

Around a third of patients with irritable bowel syndrome have persistent diarrhoea (IBS-D). A study by Gecse and colleagues shows that these are rather different from other types of IBS. Faecal supernatants from patients with IBS-D were shown to have increased levels of proteolytic activity, similar to those seen in ulcerative colitis (see fig). No increase was noted in the other IBS subgroups (constipation and alternating subtypes) nor in those with infectious diarrhoea. These proteases do not appear to be of pancreatic origin because pancreatic elastase showed a quite different pattern. Polymorphonuclear leucocytes also seem unlikely to be the source of the enzymes as calprotectin and polymorph elastase were only elevated in ulcerative colitis and infectious diarrhoea. Mast cells appear to be the most likely source. The authors showed that these faecal supernatants induced visceral hypersensitivity in mice. The effect appears to be mediated through the protease-activated receptor type 2 (PAR-2)



Increased total proteolytic activity in faecal supernatants of patients with irritable bowel syndrome (IBS) with diarrhoea (IBS-D) or ulcerative colitis (UC) but not other types of IBS (IBS with constipation (IBS-C) or alternating subtypes (IBS-A)) nor those with infectious diarrhoea (INF). *p<0.05, **p<0.01.

because the effect was absent in PAR-2 deficient mice and inhibited by protease inhibitors. Faecal supernatant proteases also increased colonic permeability. This study opens the way to novel treatments including protease inhibitors or mast cell stabilisers in IBS. ***See page 591***

Limited role of rectal compliance in treatment-refractory constipation in adolescents

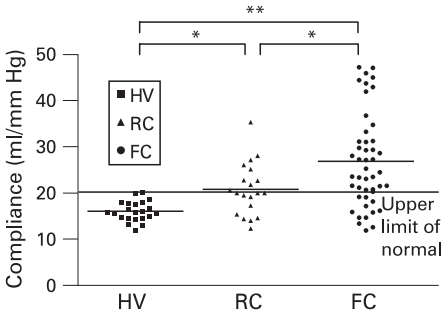
Functional constipation (FC) is very common in children. Approximately a third of these children are unresponsive to conventional treatment. Abnormal rectal function due to increased distensibility (compliance) has been proposed to be an important factor behind treatment resistance in FC. In this study by van den Berg and colleagues, rectal compliance in adolescents with FC (n = 47), patients who had recovered successfully from FC (n = 20) and healthy volunteers (n = 22) were compared. Patients with FC had higher rectal compliance than both patients who had recovered from FC and healthy volunteers (see fig). Patients who had recovered from FC had higher compliance than healthy volunteers despite the fact that they had been free of symptoms for at least 4 years and 45% still had abnormal rectal compliance (>95th percentile in healthy volunteers); 75% of patients with FC had abnormal rectal compliance. This study shows that increased rectal compliance is common in patients with FC but its role in treatment-refractory FC seems limited as complete recovery is possible despite increased rectal compliance. ***See page 599***

Bradykinin B_1 receptors—an important spasmogen in the human gallbladder—is upregulated in acute cholecystitis

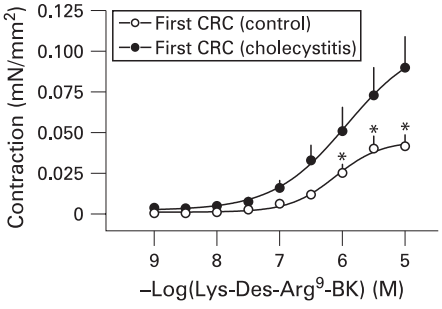
Severe pain is a key symptom in acute cholecystitis. Spasms, produced by gallbladder smooth muscle contractions in order to expel stones, are proposed to greatly contribute to pain in patients with cholecystitis. Antagonising these contractions, therefore, seems to be a logical treatment alternative for biliary colic. Recently, bradykinin B_2 receptors have been demonstrated in the human gallbladder and activation of the receptors leads to contractions, especially in acute cholecystitis. In the study by Andre and coworkers, the role of bradykinin B_1 receptors in the control of contractions in normal and inflamed human gallbladder was evaluated. Lys-Des-Arg^9-bradykinin, a selective B_1 receptor agonist, dose-dependently contracted strips from normal gallbladders but its effect was even more pronounced in inflamed gallbladders (see fig). The effect was reduced by a selective B_1 receptor antagonist but not by antagonism of bradykinin B_2 or tachykinin receptors, atropine or indomethacin. Moreover, B_1 receptor mRNA levels were clearly higher in cholecystitis smooth muscle specimens than in control tissues. Based on these findings, antagonists of bradykinin B_1 receptors seems to be a potential treatment option to control pain in acute cholecystitis. ***See page 628***

Inhibitory effects of oxidised lipids in pancreatitis-associated ascitic fluid on PPARγ anti-inflammatory effects

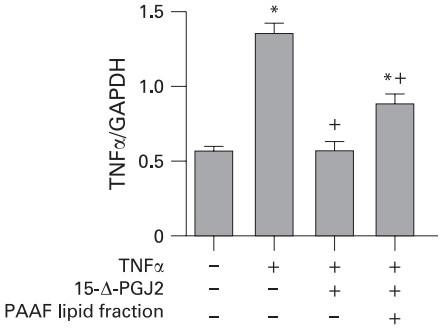
Acute pancreatitis is associated with severe systemic features including shock and renal, respiratory and hepatic failure, which are thought in part to be due to an excess of inflammatory cytokines. Some studies have suggested that pancreatitis-associated ascitic fluid (PAAF) is an important part of the inflammatory process. Release of lipolytic pancreatic enzymes into the peritoneal cavity generates high local concentrations of free fatty acids as peritoneal fat undergoes autodigestion. The study by Gutierrez and coauthors examines the lipid fraction of PAAF in rats in which pancreatitis was induced by intraductal administration of bile acids. High levels of lipid peroxidation were observed in PAAF but not in white adipose tissue in either controls or in those with acute pancreatitis. The lipid fraction of PAAF induced cellular toxicity. Furthermore, when macrophages were treated with PAAF this inhibited the anti-inflammatory effect of the peroxisome proliferator-activated receptor (PPAR) γ agonist 15-deoxy-prostaglandinJ_2, as seen by increased tumour necrosis factor α mRNA levels (see fig, right hand column). PAAF also impaired the binding of PPARγ with DNA which normally induces an anti-inflammatory effect. This interference with these endogenous anti-inflammatory mechanisms may result in an exacerbation of the systemic inflammatory response observed during severe acute pancreatitis and could be a treatment target. ***See page 642***



Rectal compliance in healthy volunteers (HV), patients with functional constipation (FC) and patients recovered from FC (RC). *p<0.05, **p<0.001.



Concentration–response curves (CRCs) to a bradykinin B_1 receptor agonist in isolated strips of normal and inflamed human gallbladder.



Pancreatitis-associated ascitic fluid (PAAF) lipid fraction partially blocked the depression of tumour necrosis factor (TNF) α mRNA induced by the peroxisome proliferator-activated receptor (PPAR) γ agonist 15-deoxy-prostaglandinJ_2. *p<0.05 vs control, +p<0.05 vs TNF α treated.