Retinoids, bile acids and PPARs in Barrett’s oesophagus

Intestinal metaplasia of the oesophagus (Barrett’s oesophagus) is the most important risk factor for oesophageal adenocarcinoma. Although the role of mixed bile and acid gastro-oesophageal reflux is well established, the contribution of nuclear receptor signalling in the pathogenesis of Barrett’s oesophagus remains largely unknown. The recent article by Chang et al. (Gut 2007;56:906–17) showing that retinoid acid and lithocholic acid play an important role in the development of oesophageal intestinal metaplasia, is of particular interest, because retinoid receptors are also heterodimeric partners of multiple nuclear receptors.

We recently published a report demonstrating the over-expression of the nuclear bile acid receptor FXR in Barrett’s oesophagus and its possible role in the regulation of apoptosis.1 Newly obtained results from our laboratory indicate that also other nuclear receptors, such as peroxisome proliferator-activated receptors alpha and gamma (PPARα and γ), are up-regulated in Barrett’s oesophagus. Both FXR and PPARs are transcription factors which are abundantly expressed in the lower digestive tract, and are activated by bile, fatty acids and retinoids (by virtue of their heterodimeric form with the retinoid X receptor, RXR).2 The observations by Chang et al. and our findings, suggest that the retinoid signalling cascade is involved in the pathogenesis of Barrett’s oesophagus and could be mediated by nuclear receptor signalling mechanisms.

Biopsy samples were obtained at endoscopy from normal oesophagus, Barrett’s oesophagus and oesophageal adenocarcinoma (six patients per group). Expression of PPARα and PPARγ was quantified by real time PCR, (primers F 5′-GAGCTCCACCGGTTTTGGA CTTGAAC-3′; R 5′-CCAAGCTGCTCCAGCCCAT-3′ and F 5′-CCAAGCTGCTCCAG DAAAC-3′; R 5′-AGCGGGTGAAGACTCATC-3′), respectively) using 18S ribosomal RNA for normalisation. Immortalised cells derived from Barrett’s oesophageal epithelium (CP-18521) were cultured as previously described3 and treated with agonists or antagonists of PPARα (10 μmol/l WY-14463 and 20 μmol/l MK886, respectively) and of PPARγ (20 μmol/l rosiglitazone and 30 μmol/l PD066235, respectively). Apoptosis in Barrett’s derived cells was assessed by flow cytometry after labelling with 7-amino-actinomycin D. Results were compared using the Student t test and a p value <0.05 was considered statistically significant.

The expression of both PPARα and PPARγ was significantly higher in Barrett’s oesophagus compared to normal mucosa and adenocarcinoma of the oesophagus (fig. 1). This is in agreement with several studies showing that PPARs are present in intestinal epithelial cells, where they are involved in the regulation of inflammatory processes and apoptosis.3

Treatment with the PPAR antagonists MK886 and PD066235 significantly increased the proportion of apoptotic CP-18521 cells (fig. 2), suggesting that PPAR signalling may contribute to the regulation of apoptotic processes in Barrett’s oesophagus. Treatment with PPAR agonists WY-14463 or rosiglitazone did not affect apoptosis.

These new data show that PPARα and PPARγ are up-regulated in Barrett’s oesophagus and suggest that they contribute to the regulation of apoptosis. Since these receptors constitute heterodimeric units with RXR, our data extend those of Chang et al., supporting the hypothesis that retinoids, bile acids and fatty acids play an active role in the pathogenesis of Barrett’s oesophagus.

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Figure 1 Expression of PPARα and PPARγ in Barrett’s oesophagus and oesophageal adenocarcinoma relative to normal oesophagus, as quantified by real time PCR. *p<0.05.

Figure 2 Apoptosis in Barrett’s derived cultured cells in controls and after treatment with the PPARα and PPARγ antagonists MK886 and PD066235, respectively, as assessed by flow cytometry after labelling with 7-amino-actinomycin D. *p<0.05.

Genetic testing is ready to change the diagnostic scenario of lactose malabsorption

We write in response to the article by Swallow (Gut 2006;55:131) in which a DNA test was considered premature for diagnosing hypolactasia. We would also like to comment on the diagnostic conclusions of Ransinpera et al1 with regard to younger children.

Recently, the C/T-13910 polymorphism on chromosome 2q21 in Northern European populations has been found to be completely associated with lactase activity2 and proposed as a new diagnostic tool in adult-type hypolactasia.3 Although in some African groups other polymorphisms can be present (Swallow et al), the same polymorphism has also been found in non-Northern European populations.4,5

The lactose breath test (BT) is an indirect test for lactose malabsorption which is considered the most reliable, non-invasive and economical technique, although it bears a reasonably high risk for false-negative results.6 Some researchers have proposed the jejunal biopsy as gold standard. However, it seemed too invasive for the diagnosis and its results can be influenced by the uneven dissemination of lactase activity throughout the small intestine mucosa.

In subjects older than 12 years of age, genetic testing (GT) showed a sensitivity of 93% and a specificity of 100% when compared with jejunal biopsy.7 In a recently published work,8 we have demonstrated in adult Mediterranean subjects an excellent correlation between the BT and C/T-13910 polymorphism. A high degree of sensitivity and specificity (100% and 96%, respectively) was obtained by comparing GT with a combination of different BTs and clinical assessment. Moreover, in a recent Canadian report,9 the sensitivity and specificity of the lactose BT (80% and 100%) and lactose tolerance test (93% and 87%) were calculated with respect to GT which was considered a new gold standard.

For these reasons, a new diagnostic algorithm could be proposed for lactose malabsorption:

- GT may complement in several aspects the BT, improving the diagnosis of adult-type hypolactasia. In all subjects

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with a negative lactose BT, GT provides an unambiguous result permitting the exclusion of false-negative results (such as low hydrogen producers) and avoiding the execution of further tests (lactulose or methane BTs).

- GT can also be useful in defining those individuals with a borderline value of lactose BT (values comprised between 10 and 20 ppm of H2).

- Moreover, secondary causes of hypolactasia may be suspected in subjects with a positive BT and a C/T-13910 variant associated with lactase persistence. This latter diagnostic objective is presumably more important in populations with a low prevalence of hypolactasia. In our epidemiological reality where up to 85% of subjects are lactate malabsorbers, the investigation of a secondary hypolactasia could be unnecessary.

- Finally, according to various lines of evidence, the decline of lactase activity and the onset of adult-type hypolactasia should be evident from 8–12 years onwards. In younger subjects, GT should not be recommended, while the lactose BT remains of paramount utility in diagnosing secondary hypolactasia. Therefore, we are not in agreement with Ransinpera et al., when they affirm that in younger children, genotyping may help to exclude adult-type hypolactasia as a cause of abdominal symptoms, because a lactase activity is already present.

Our ongoing experience supports the diagnostic efficacy of GT also in non-Northern European populations.

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Author’s response
Dr Usai Satta and colleagues remarked on our diagnostic conclusions on the use of genetic testing (GT) that is based on the genetic polymorphism C/T-13910 on chromosome 2q21 with regard to younger children. They recommend that lactose breath tests should be the first-line diagnostic method in children under 8 years of age. We would point out that the performance of hydrogen breath tests is not always accurate in younger children, and there are limited data on these tests in children. Further, this investigation is laborious and should be conducted under the surveillance of trained personnel.

It should be remembered that the decline of the intestinal lactase level occurs on an individual basis and cannot be foreseen so far in those with a genetic predisposition for hypolactasia. By the age of 8 years the intestinal lactase level is low in the majority of the children with genotype C/C-13910 associated with hypolactasia, and the avoidance of milk is common. Parents easily suspect milk as a causative agent for abdominal symptoms in their children in countries where dairy products are widely used. GT is easy to perform and it does not need to be repeated. In younger children, GT is excellent in excluding the presence of genetic hypolactasia with a negative predictive value of 98% in all age groups. Therefore, in populations with a high prevalence of lactase persistence, GT is a clinical aid in excluding genetic hypolactasia even in younger children.

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Avoiding the V-word: Is Volume therapy in hepatorenal syndrome killed by definition?

It is generally believed that the hepatorenal syndrome (HRS) is a functional kidney disorder resulting from a disturbed and hyperdynamic circulation leading to central hypovolaemia. Yet there seems to be a strong reluctance to regard it as amenable to volume resuscitation. In this context, the most striking change to the previous definition of HRS Type 1, proposed by the recent consensus workshop (Gut 2007;56:1310–8) is the inclusion among the diagnostic criteria of a failure to respond to plasma expansion with up to 1 g of albumin per kg body weight per day for 2 days. The amount itself is arbitrary and must result in a substantial, if not individually adjusted, increase in total plasma volume.

The authors do not fail to point out that there are no dose/effect studies concerning the use of albumin in HRS. So how do we know that none of the remaining HRS patients would respond to, say, double the amount of albumin for three days?

It is notoriously difficult to predict fluid-responsiveness in patients with hyperdynamic circulatory failure, and we doubt that in any of the relevant studies on HRS haemodynamic monitoring has been adequate to exclude fluid responsiveness of cardiac output and renal perfusion in the study population.

Convincing data on this issue certainly has not been published. Yet the lack of response of HRS to volume resuscitation has become a dogma so strong that even investigators confronted with findings in HRS patients which may be largely explained by a relative hypovolaemia, do not even discuss the possibility. In their own publication two of the Ascites Club’s members demonstrated that decreased pulmonary arterial wedge pressure (PAWP) and reduced cardiac output (CO) in cirrhotic patients were associated with the development of HRS Type 1 and a worse outcome. They attributed this to myocardial failure. However, the finding of low PAWP and decreased CO characterises hypovolaemia, not myocardial impairment, where PAWP and CO are decreased.

Convincing evidence on this issue certainly has not been published. Yet the lack of response of HRS to volume resuscitation has become a dogma so strong that even investigators confronted with findings in HRS patients which may be largely explained by a relative hypovolaemia, do not even discuss the possibility. In their own publication two of the Ascites Club’s members demonstrated that decreased pulmonary arterial wedge pressure (PAWP) and reduced cardiac output (CO) in cirrhotic patients were associated with the development of HRS Type 1 and a worse outcome. They attributed this to myocardial failure. However, the finding of low PAWP and decreased CO characterises hypovolaemia, not myocardial impairment, where PAWP is increased.

Hypovolaemia is intrinsically tied to known triggers of HRS, be it infection, over-zealous use of diuretics, paracentesis or haemorrhage and the prophylactic use of colloids to prevent HRS under these conditions is no matter of debate. There is also little doubt on the importance of volume