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Grant awarded £29,887 (1 Year)

Investigation of the importance of the gastrin family of peptides and gastrin/CCK_B receptor in inflammatory bowel disease.

Over the years, many investigators have studied whether hormones and growth factors play a role in the development and treatment of inflammatory bowel disease (ulcerative colitis and Crohn's disease). One family of such hormones, the gastrin family, has however not been extensively investigated in inflammatory bowel disease and we propose that it is now timely to do so.

The main function of the hormone gastrin is to regulate the production of acid in the stomach, in order to aid digestion of food. Gastrin is however produced from a larger molecule called preprogastrin via intermediate molecules called progastrin and glycine-extended gastrin. Over recent years, several transgenic (genetically manipulated) mice have been created that express increased levels of various hormones from the gastrin family within their bloodstream. Analysis of these mice has suggested that the gastrin family of hormones exert important effects upon the bowel as well as the more well known effects on the stomach.

We have been recently studying the effects of radiation (which causes damage to the intestine) in two strains of transgenic mice in our laboratory. One strain has high blood levels of progastrin and the other has high blood levels of gastrin. We have shown that cells in the bowel (colon) of progastrin overexpressing mice continue to divide after radiation treatment, whereas the same cells in ordinary mice stop dividing completely. In addition we have shown that the effects of high doses of radiation (which normally cause inflammation in the intestine resulting in diarrhoea) are diminished in mice that express high levels of gastrin. This effect in mice with high blood levels of gastrin seems to result from increased expression of the gastrin receptor on the surface of colonic cells following radiation treatment. It therefore appears that following injury to the bowel (by radiation), colonic cells express the gastrin receptor on their cell surface; this allows the hormone gastrin to bind and exert effects upon the cells, causing them to be more likely to survive the consequences of injury.

We would like to suggest that this hypothesis is not only true for the effects of radiation in mice, but also occurs in the human bowel when it is injured in a different way by inflammatory bowel disease. It is important to investigate this hypothesis, because drugs are already available which can cause increased levels of gastrin in humans. These drugs are currently used for conditions such as duodenal ulcer, are safe and are widely available. There have already been two reports showing that small numbers of patients with inflammatory bowel disease have responded favourably to this type of treatment. However, these findings have not been assessed scientifically by a clinical trial.

In order to investigate the importance of the gastrin family of hormones and the gastrin receptor in inflammatory bowel disease we plan to conduct experiments using both transgenic mice and biopsies obtained from patients with inflammatory bowel disease. We will treat mice with a chemical that causes colitis and will investigate whether the severity of colitis is reduced in mice that express high levels of either gastrin or progastrin. In addition we will investigate whether cells from biopsies of patients with inflammatory bowel disease express higher concentrations of the gastrin receptor than those from patients with a normal colon. We will also see whether the colonic cells from inflammatory bowel disease patients behave differently when treated with gastrin in a test tube.

These experiments will determine whether the expression of the gastrin receptor is increased in the bowel of patients with inflammatory bowel disease and whether treatment of inflammatory bowel disease patients with drugs that increase the level of gastrin in the bloodstream is likely to have a beneficial effect. If our hypothesis is confirmed, we would propose to investigate matters further by means of a clinical trial of drugs that increase blood gastrin levels in patients with inflammatory bowel disease.