Acetorphan and diarrhoea

Editor,—We were interested to read the paper of Baumer (Gut 1992; 33: 753–8) regarding the antiserotonin effects of enkephalinase (neutral endopeptidase 24.11) inhibition with acetorphan in cathartic and infectious diarrhoea in man and would like to stress another role for enkephalinase enzymes in down regulating the inflammatory response.1

Enkephalinase (neutral endopeptidase 24.11) reduces the response of neutrophils to inflammatory peptide stimuli including the bacterially derived F-met peptides. Peptidase enzymes are thought to protect the gut from the inflammation induced by bacterial peptides.2 We have studied enkephalinase activity in peripheral blood neutrophils in ulcerative colitis3 patients with ulcerative colitis showed enkephalinase activity of 1.0±0.3×10^3 Mmol/min/10^6 neutrophils (mean±SD) in contrast healthy volunteers showed enkephalinase activity of 2.6±0.8 (mean±SD)×10^3 Mmol/min/10^6 neutrophils (mean±SD).3 We have identified the major mucosal peptidase responsible for F-Met-Leu-Phe hydrolysis as a carboxypeptidase which is down regulated in Crohn’s disease and have also suggested a role for a F-Met deformylase and a peculiar F-Met aminopeptidase. By contrast, a role for enkephalinase, whose activity in mucosa is greater than in neutrophils, was not shown in this study. In addition, it seems likely that bacterial colonisation and pullulation within the intestinal lumen facilitates the crossing of bacterial pro-inflammatory peptides.3 This result, the use of a purely antiinflammatory agent such as the enkephalinase inhibitor acetorphan as an antiinflammatory agent seems preferable to traditional opiate like antidiarrhoeals,4 both in rodents5 and humans.6

The suggested role of enkephalinase in down regulating inflammatory response in airways, through degradation of tachykinins, has also been challenged recently as the inhibitor acetorphan given to volunteers with asthma had no deleterious effects.7 Hence the antiinflammatory role of the peptidase is far from established.

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Reply

Editor,—The proposal by Cole and Hawkey for a role of enkephalinase (membrane metalloendopeptidase, EC 3.4.24.11) in the degradation of bacterial F-Met-Phe-Leu and other proinflammatory peptides in patients with ulcerative colitis seems an interesting suggestion. We feel, however, that this view is supported by their data1 and, furthermore, seems unlikely. First, the assay they used to establish a significant change (p=0.048) in a small sample of patients (n=6) is incorrect as thorphan is used at a concentration of 10 000 times higher than actually required for a specific assay.2 We have also found that this experimental condition leads to an overestimation of the specific enzyme activity of isolated human neutrophils by up to 50%. Secondly, among the six patients described by Cole et al.,1 two were receiving steroids, three steroid enema, five oral salicylates, and four aza-thioprine and it would seem, therefore, rather premature to attribute any change in their neutrophils to the disease rather than to such treatments. Thirdly, it seems misleading to study inactivation of pro-inflammatory F-Met peptides by peptidases of neutrophils rather than by intestinal mucosa. Indeed, proinflammatory F-Met peptides generated by intestinal bacteria may play a part in intestinal inflammatory disorders if they cross the epithelial barrier in which local peptidases seem to play a critical role. Hence Chadwick et al.2 have identified the major mucosal peptidase responsible for F-Met-Leu-Phe hydrolysis as a carboxypeptidase which is down regulated in Crohn’s disease and have also suggested a role for a F-Met deformylase and a peculiar F-Met aminopeptidase. By contrast, a role for enkephalinase, whose activity in mucosa is greater than in neutrophils, was not shown in this study. In addition, it seems likely that bacterial colonisation and pullulation within the intestinal lumen facilitates the crossing of bacterial pro-inflammatory peptides.3 This result, the use of a purely antiinflammatory agent such as the enkephalinase inhibitor acetorphan as an antiinflammatory agent seems preferable to traditional opiate like anti-diarrhoeals,4 both in rodents5 and humans.6

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NOTES

National Association for Colitis and Crohn’s Disease

NACC is pleased to invite applications for the 1993 grant awards. Projects are invited on any aspect of inflammatory bowel disease. NACC is particularly keen to encourage not only high quality mainstream research, but also welcomes applications which may be considered as realistic ‘what if’ research projects. These projects will likely be smaller, relatively inexpensive applications which might be viewed less favourably by larger, less specialised organisations. Although all applications are assessed together, NACC wishes to encourage projects which address social and quality of life issues of inflammatory bowel disease where methodology remains difficult.

The closing date for applications is Friday 30 April 1993. Further details are available from Dr P B McIntyre, Honorary Secretary, Medical Advisors NACC, Queen Elizabeth II Hospital, Howlands, Welwyn Garden City, Herts AL7 4HQ.

Barcelona ‘93 – II United European Gastroenterology Week

This will take place from 19 to 24 July 1993 in Barcelona, Spain. Further information from Prof J R Malagelada, c/o UNICONGRESS, Calle Galvet 55-57 (4th floor), 08021 Barcelona, Spain (Tel: 34 3 414 03 22; fax: 34 3 414 02 51).
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