

ORIGINAL ARTICLE

Gastrin releasing peptide receptor expression is decreased in patients with Crohn's disease but not in ulcerative colitis

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J Clin Pathol 2004;57:1047-1051. doi: 10.1136/jcp.2003.014993

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Accepted for publication 13 May 2004

Background: Gastrin releasing peptide (GRP) and neuromedin B are bombesin (BN)-like peptides involved in regulating motility and inflammation in the gastrointestinal tract, which may be useful in treating inflammatory bowel disease (IBD). Three bombesin-like peptide receptors have been reported, but no studies have investigated their localisation in normal and inflamed human intestine.

Aim: To localise and characterise BN receptors in normal intestine and to see whether this is modified in IBD.

Methods: Full thickness intestinal tissue samples were collected from 13 patients with Crohn's disease (CD), 11 with ulcerative colitis (UC), and 19 controls. BN receptor expression was characterised and quantified with storage phosphor autoradiography using BN, GRP, neuromedin B, and the synthetic analogue BN(6-14) as ligands.

Results: Only BN receptor type 2 (high affinity for GRP) was present in intestinal tissue. Minimal BN binding was detected in the mucosa. In normal colonic smooth muscle, mean BN binding was 336 fmol/g tissue in longitudinal muscle, including the myenteric plexus, and 71 fmol/g in circular muscle. In CD, colonic smooth muscle BN binding was significantly decreased (longitudinal muscle, 106; circular muscle, 19 fmol/g), in contrast to UC (377 and 62 fmol/g, respectively). In CD, a small (not significant) decrease was seen in ileal muscle compared with controls (111 v 169 and 18 v 32 fmol/g tissue for longitudinal and circular muscle, respectively).

Conclusions: Only the GRP receptor is expressed in human intestine; expression is highest in longitudinal muscle and myenteric plexus of the colon. Expression is decreased in inflamed and non-inflamed colon of CD, but not in UC.

Bombesin (BN), a 14 amino acid peptide, was originally isolated from the skin of the amphibian *Bombina orientalis*.¹ Gastrin releasing peptide (GRP) and neuromedin B (NMB) belong to the BN-like peptide family in mammals.² In the gastrointestinal tract, GRP is found in neurones in the human intestine and stomach. The highest amounts of NMB-like immunoreactivity are found in nerves in the circular smooth muscle of the oesophagus and rectum. Peptides from the BN family exert a variety of central and peripheral functions. In the gastrointestinal tract, they stimulate secretion from endocrine (gastrin, somatostatin) and exocrine cells (pancreas), exert direct effects on smooth muscle, and they have mitogenic effects.³⁻⁴ In vitro studies have shown that BN-like peptides also have immunoregulatory functions: GRP is a potent chemoattractant of macrophages and lymphocytes,⁵ and is also able to enhance the phagocytic process in macrophages⁶ and to stimulate cellular cytotoxicity and natural killer activity in human peripheral blood and lamina propria mononuclear cells.⁷⁻⁹

"In vitro studies have shown that bombesin-like peptides also have immunoregulatory functions"

In humans, there are three receptors for the BN-like peptides, namely: the NMB receptor, with a high affinity for NMB¹⁰; the GRP receptor, with a high affinity for GRP¹¹⁻¹³; and the BN receptor subtype 3 (BRS-3),¹⁴⁻¹⁵ for which the natural ligand is not yet known. All three receptors belong to the family of seven transmembrane domain G protein coupled receptors. In rats, BN binding sites were localised to the circular muscle of the gastric fundus and antrum, the submucosal layer of the small intestine, and the longitudinal

and circular muscle and submucosal layers of the colon.¹⁶ In humans, the NMB receptor is found in the muscularis mucosa of the oesophagus, whereas the GRP receptor is present in the pancreatic acini.¹⁷ In addition to being abundant in the oesophagus and pancreas, BN receptors are also present in ileal and colonic smooth muscle, but not in epithelial cells.¹⁸⁻²⁰ Until recently, little was known about BRS-3 because of the lack of a ligand. Recently, a synthetic ligand ([D-Phe⁶, β-Ala¹¹, Phe¹³, Nle¹⁴]-BN(6-14); BN(6-14)) became available, which binds all three BN receptors, so that by using GRP and NMB as competitive ligands all three receptors can be distinguished.²¹⁻²² In this way, BRS-3 has been demonstrated in human pancreatic islets.²³ However, no studies with BN(6-14) have been performed to characterise the BN receptor family in the normal human gastrointestinal tract.

Several studies have shown the ectopic expression of BN receptors in human breast, prostate, lung, and gastrointestinal carcinomas,¹³⁻¹⁹⁻²⁴⁻²⁷ and the therapeutic use of BN antagonists has been suggested. Furthermore, technetium BN analogues have already been used for diagnostic purposes in clinical studies.²⁸⁻²⁹ In addition, BN and its receptors might be of importance in inflammatory conditions. Inflammatory bowel disease (IBD) is an inflammatory disease of the gastrointestinal tract. Crohn's disease (CD) and ulcerative colitis (UC) are two different forms of IBD: CD affects the full thickness of the wall of the colon or the small intestine, whereas UC primarily affects the mucosa of the colon.

Abbreviations: BN, bombesin; BN(6-14), [D-Phe⁶, β-Ala¹¹, Phe¹³, Nle¹⁴]-bombesin(6-14); BRS-3, bombesin receptor subtype 3; CD, Crohn's disease; GRP, gastrin releasing peptide; IBD, inflammatory bowel disease; NMB, neuromedin B; TNBS, 2,4,6-trinitrobenzenesulfonic acid; UC, ulcerative colitis

Disturbed intestinal and colonic motility, diarrhoea, and weight loss clinically characterise both diseases. Histologically, the affected tissue shows ulceration and the infiltration of inflammatory cells.³⁰

Because the effects of BN are established only after binding with its receptor, it is important to know the BN receptor status of patients with IBD. It is known that the expression pattern of receptors for other neuropeptides, such as substance P, is altered in IBD.³¹ In addition, Mantyh *et al* detected binding sites for BN in IBD.³²

The aim of our present study was to localise and quantify all three receptors for BN in the human intestinal tract and to study whether this expression is modified in the inflamed and non-inflamed intestine of patients with IBD.

MATERIAL AND METHODS

Tissue samples

Colonic or ileal tissue samples were collected at the Leiden University Medical Centre, the Netherlands. Thirteen patients with CD and 11 with UC were included in our study and tissue was taken from both the inflamed and non-inflamed areas, as indicated by the pathologist. As normal controls, tissue was taken at least 10 cm from the affected site of 19 patients with a non-inflammatory related disease, mainly colonic tumours. Table 1 summarises the patients' characteristics. After surgical resection, full thickness tissue samples were immediately embedded in Tissue-Tek® OCT compound and frozen on dry ice. Tissue was stored at -80°C until use.

Storage phosphor autoradiography

Storage phosphor autoradiography was used to identify the presence of receptors. The technique gives information on the localisation, quantity, and the binding characteristics of the receptors. Cryostat tissue sections ($14\ \mu\text{m}$) were cut at -20°C , mounted on gelatin coated glass slides, and stored overnight at -80°C . Storage phosphor autoradiography was performed according to the protocol described previously.³³ Slides were incubated with $75\ \text{pM}$ ^{125}I -[D-Tyr⁶, β -Ala¹¹, Phe¹³, Nle¹⁴]-BN(6-14) for cold saturation studies or ^{125}I -[Tyr⁴]-BN for quantification studies (Perkin Elmer Life Science, Boston, Massachusetts, USA). The first ligand has a high affinity for all three human receptors and the second binds preferentially with the GRP receptor. BN(6-14) (Polypeptide Laboratories GmbH, Wolfenbuttel, Germany), BN, GRP, and NMB (Bachem AG, Bubendorf, Switzerland) were used as non-radioactive ligands to detect non-specific binding. Dose inhibition curves were made using different concentrations ($1\ \mu\text{M}$ – $1\ \text{pM}$) of the non-radioactive ligands (cold saturation studies) to determine which receptor types were present. The dissociation constant, K_d , was determined using the non-linear least squares curve fitting program LIGAND³⁴ to obtain information about the characteristics of the receptor. Binding was quantified with a storage phosphor screen and ImageQuant® software (Molecular Dynamics, Sunnyvale, California, USA). Slides with $10\ \mu\text{l}$ drops of different concentrations of radiolabelled ligand were used for standardisation. Rat brain sections were used as a positive control. Binding was expressed as fmol/g tissue. Serial

sections were stained with haematoxylin and eosin to distinguish the different layers in the intestine.

Data analysis

Data were expressed as mean (SEM). An unpaired Student's *t* test was used for statistical assessment of differences between means. Values of $p < 0.05$ were considered significant.

RESULTS

Localisation of BN binding sites

In the colon and ileum of control patients BN binding was seen in the longitudinal smooth muscle layer and the myenteric plexus. Binding to the circular smooth muscle layer was weaker. A low binding signal was found in the mucosa of the colon, but not in the ileum. A similar distribution pattern was seen in the colon and ileum of patients with IBD, but the intensity in the colonic longitudinal and circular smooth muscle of patients with CD was lower than that seen in controls and patients with UC. Figure 1 provides a representative picture of the binding pattern for normal colon and the inflamed colon of a patient with CD.

Identification of binding sites

Cold saturation inhibition curves using the universal ligand ^{125}I -[D-Tyr⁶, β -Ala¹¹, Phe¹³, Nle¹⁴]-BN(6-14) were performed to identify the BN receptor types present in the intestine of control subjects and patients with IBD. Figure 2 shows an inhibition curve of BN receptors in a control colon; this curve is also representative of the curves seen in the ileum and in patients with IBD. This inhibition curve shows that the binding sites have a high affinity for GRP and BN(6-14), but a lower affinity for NMB, which is characteristic of the GRP receptor. No receptors with a high affinity for NMB or only a high affinity for BN(6-14) (BRS-3) were detected in the human intestinal tract. The K_d for the affinity of BN binding was calculated using LIGAND software. For some tissues a two site model was possible, but this was never significantly better than the one site model, and the K_{d2} was always extremely high (range, 235–15236nM). The mean K_{d1} for BN was 2.54nM.

Quantification of BN binding sites in control patients

Binding detected by storage phosphor autoradiography was quantified using ImageQuant® software. In colonic smooth muscle of the control patients, the mean (SEM) BN binding was 183 (43) fmol/g tissue, but a pronounced difference was seen between the two muscle layers. Mean (SEM) BN binding in the longitudinal muscle, including the myenteric plexus, was 336 (66) fmol/g tissue, whereas binding in the circular muscle was only 71 (20) fmol/g tissue ($p < 0.01$). Significantly lower binding was found in the ileum of control patients compared with the colon. The difference in binding between the longitudinal and circular muscle seen in the colon was also seen in the ileum: mean (SEM) binding was 169 (54) fmol/g and 32 (11) fmol/g ($p = 0.02$), respectively. In the mucosa, only the colon showed a weak binding (mean, 10; SEM, 4 fmol/g tissue).

Table 1 Patient characteristics

Group	N	Age range in years (mean)	Sex (M/F)	Location (ileum/colon)	Inflammation (yes/no)	No anti-inflammatory drugs
Controls	19	34–74 (55)	10/9	8/12	0/20	19
CD	13	18–73 (37)	3/10	9/8	10/7	2
UC	11	19–72 (40)	4/7	0/13	8/5	2

CD, Crohn's disease; UC, ulcerative colitis.

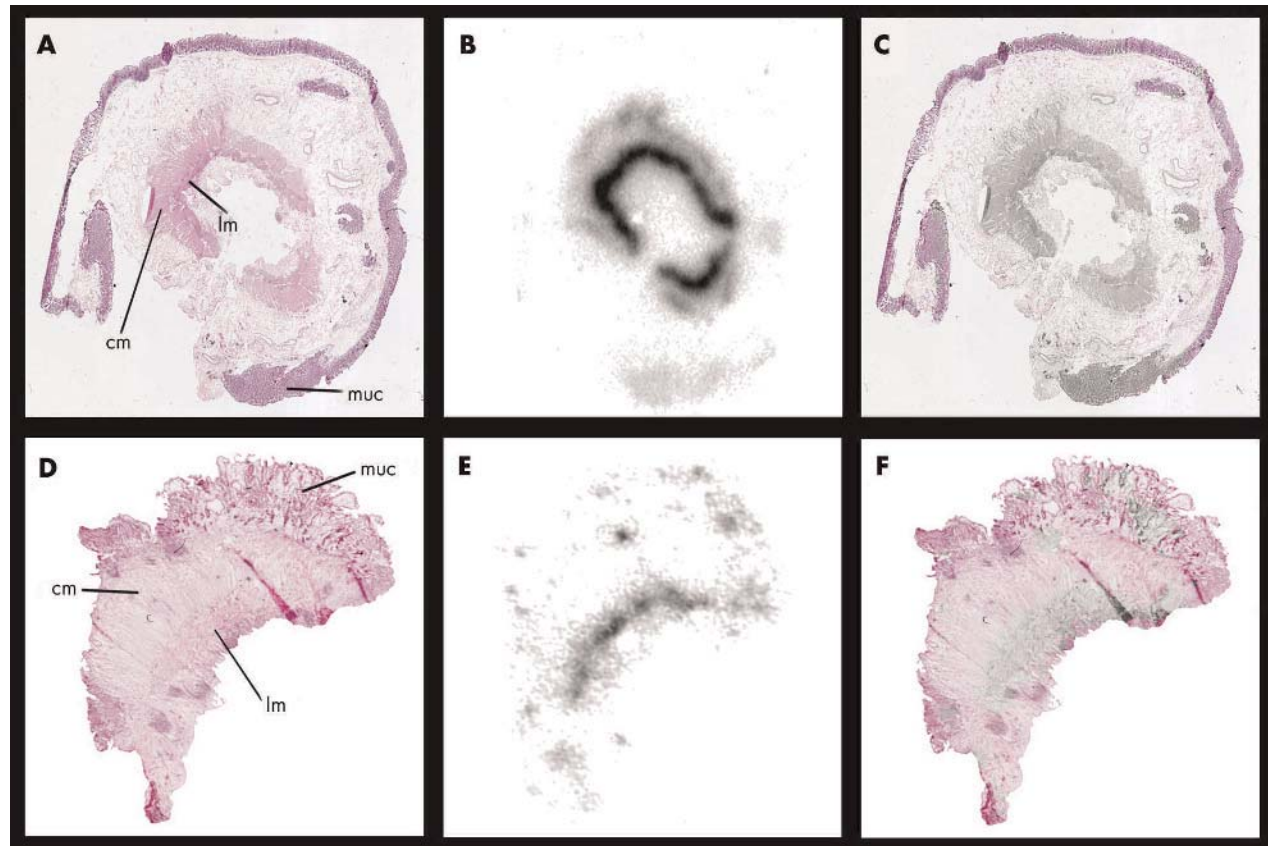


Figure 1 ^{125}I -BN binding to (A–C) control and (D–F) inflamed coeliac disease colonic tissue. (A, D) Haematoxylin and eosin staining. (B, E) Specific binding of ^{125}I -BN on the serial sections; therefore, the non-specific binding image is subtracted from the total binding image. The intensity of the greyscale equals the amount of binding sites. (C, F) The precise location of the BN binding sites is shown by merging the binding image with the haematoxylin and eosin stained image, which gives a qualitative result. BN, bombesin; cm, circular muscle; lm, longitudinal muscle; muc, mucosa.

Quantification of BN binding sites in patients with IBD

Binding to both muscle layers was greatly decreased in the colon of patients with CD. In the circular muscle, mean (SEM) BN binding was 19 (4) fmol/g tissue, and in the longitudinal muscle (including the myenteric plexus) binding was 106 (30) fmol/mg tissue; binding at both these sites was significantly lower than that seen in controls (fig 3). In patients with UC, such a decrease was not seen. Binding in both muscle layers was comparable with controls (mean (SEM), 62 (10) and 377 (58) fmol/g tissue; fig 3). In the ileal muscle of patients with CD there was also a small, although

not significant, decrease compared with controls (mean (SEM), 111 (20) v 169 (54) fmol/g tissue and 18 (4) v 32 (10) fmol/g tissue, for longitudinal and circular muscle, respectively).

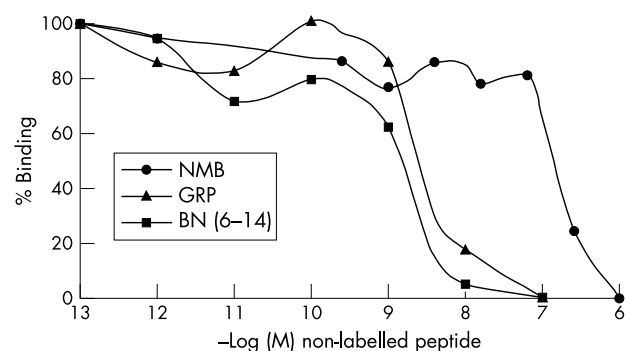


Figure 2 Competitive inhibition of ^{125}I -BN(6–14) binding to human control colon. Tissue was incubated with 75pM ^{125}I -BN(6–14) and the indicated concentration of NMB, GRP, and BN(6–14). BN(6–14), [D-Phe⁶, β-Ala¹¹, Phe¹³, Nle¹⁴]-bombesin(6–14); GRP, gastrin releasing peptide; NMB, neuromedin B.

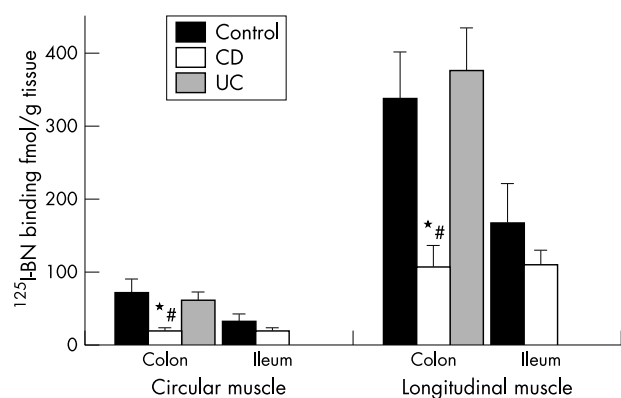


Figure 3 Quantity of ^{125}I -BN binding to smooth muscle of human colon and ileum as detected with autoradiography. Left: BN binding to circular smooth muscle of controls, patients with CD, and patients with UC. The first three bars represent colonic tissue and the last two bars ileum (12, seven, 15, eight, and nine samples, respectively). Right: NT binding to longitudinal muscle, including the myenteric plexus, of controls, patients with CD, and patients with UC. The first three bars represent colonic tissue and the last two bars ileum (12, seven, 15, eight, and eight samples, respectively). Values are means (SEM). * $p < 0.05$ compared with controls; # $p \leq 0.01$ compared with UC. BN, bombesin; CD, coeliac disease; UC, ulcerative colitis.

Within the CD and UC patient groups no differences were seen between inflamed and non-inflamed regions and there was no association with the use of anti-inflammatory drugs. Furthermore, no difference was detected between male and female patients in all three groups.

DISCUSSION

In our present study, we studied the quantity and localisation of receptors from the BN family in the mucosa and smooth muscle of the human distal intestinal tract. Both normal control patients and patients with IBD were studied. Patients with mainly colonic tumours were used as normal controls. Previous studies^{24–27} have shown that colon cancers can aberrantly express the GRP receptor, but that normal epithelium surrounding the cancer does not.

The cold saturation inhibition studies showed that there were no binding sites with a high affinity for NMB, indicating that there are no detectable amounts of the NMB receptor present in the human colon and ileum. In addition, no BRS-3 were detected in the human colon and ileum; when these receptors are present a binding curve with a high affinity for BN(6–14) and a low affinity for GRP and NMB should be seen. From these inhibition studies it can be concluded that only the GRP receptor is present in the human intestine. The highest concentrations of the GRP receptor were present in the myenteric plexus and the longitudinal smooth muscle. This finding is in agreement with a study of Rettenbacher and Reubi.¹⁸ Low numbers of binding sites were present in the mucosa of the colon only. Other studies have shown that the epithelium does not express the GRP receptor.^{18–19} The mucosal binding sites found in our study are probably found on neurones in the lamina propria or the muscularis mucosa, although the resolution of autoradiography was not high enough to confirm this. Immunohistochemical studies are needed to obtain information on this matter, but to date no antibodies for the GRP receptor are available.

“Diagnostically, the difference between bombesin receptors in the colon of coeliac disease and ulcerative colitis may be useful for the differentiation between the two diseases—for example, by in vivo receptor scintigraphy”

The receptor types present and their localisation were not altered in patients with IBD, although there was a pronounced decrease in the number of binding sites in the smooth muscle of patients with CD compared with the normal control patients. This decrease was not seen in patients with UC. The use of anti-inflammatory drugs did not seem to affect GRP receptor expression. CD and UC are both chronic inflammatory conditions of the intestine, but in patients with CD this is a transmural inflammation, whereas in those with UC only the mucosal layer is affected. The change in receptor expression in the smooth muscle of patients with CD but not in those with UC is in agreement with the involvement of the disease in the muscle. Previously, Mantyh and colleagues³² found no changes in BN binding sites in patients with IBD compared with controls; this discrepancy could be the result of the different methods used for quantification. Quantification with a storage phosphor screen, as used in our study, is more sensitive and has a higher dynamic range than quantification with film, as used by Mantyh *et al.*³²

Rat studies have shown that BN treatment attenuated TNBS (2,4,6-trinitrobenzenesulfonic acid) induced colonic damage and stimulated histopathologically apparent mucosal proliferation in rats.³⁵ Earlier, Chu *et al* showed that BN improved survival in a lethal model of methotrexate induced

Take home messages

- Of the three mammalian bombesin-like receptors only the gastrin releasing peptide (GRP) receptor is present in the human intestine
- The expression of this receptor is highest in longitudinal muscle and the myenteric plexus of the colon
- Expression of the GRP receptor is decreased in inflamed and non-inflamed colon of Crohn's disease, but not in ulcerative colitis
- At present, the clinical relevance of our findings is unknown

enterocolitis in rats, possibly by maintaining gut mucosal structure.³⁶ In the mucosa of patients with IBD very few binding sites for BN were seen. This suggests that if the administration of BN has any effect it will be seen in the human mucosa, acting via indirect mechanisms such as the release of other trophic agents—for example, neurotensin and peptide YY.

At present, the clinical relevance of our findings is unknown. BN is known to stimulate contraction of the colonic muscles. The low expression of BN receptors in the intestinal muscles of patients with CD may protect the patient against enhanced motility. Alternatively, the decrease in BN receptors may delay intestinal healing because rat studies have shown that the administration of BN protects against TNBS induced intestinal inflammation. Our study does not allow us to draw conclusions about the potential beneficial effects of BN administration or blocking of the BN receptors in CD. Diagnostically, the difference between BN receptors in the colon of CD and UC may be useful for the differentiation between the two diseases—for example, by in vivo receptor scintigraphy.

In conclusion, in the human colon and ileum the only BN receptor found is the GRP receptor. The highest expression is seen in longitudinal muscle and the myenteric plexus of the colon. This expression was decreased in inflamed and non-inflamed colon of patients with CD, but not in patients with UC, when compared with normal colon from controls.

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J Clin Pathol 2004 57: 1047-1051
doi: 10.1136/jcp.2003.014993

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