

# Sigmoid-colonic motility in health and irritable bowel syndrome: a role for 5-hydroxytryptamine

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**Abstract** Evidence suggests that sigmoid-colonic motility is increased in patients with irritable bowel syndrome (IBS). 5-Hydroxytryptamine (5-HT) plays a role in the control of motility, but its involvement in the dysmotility seen in IBS remains unclear. To investigate the relationship between platelet depleted plasma 5-HT (PDP 5-HT) concentration and sigmoid-colonic motility in patients with IBS and healthy volunteers. Pre- and postprandial PDP 5-HT concentrations were assessed while recording sigmoid-colonic motility in 35 IBS patients (aged 19–53 years, eight male) and 16 healthy volunteers (aged 18–39 years, six male). Motility was recorded using a five-channel solid-state catheter introduced to a depth of 35 cm into an unprepared bowel. 5-Hydroxytryptamine concentration was measured by reverse-phase HPLC with fluorimetric detection. Irritable bowel syndrome patients had elevated concentrations of PDP 5-HT under fasting ( $P < 0.004$ ) and fed ( $P = 0.079$ ) conditions compared with controls. Likewise, they exhibited increased sigmoid-colonic motility under fasting (activity index:  $P < 0.02$ ) and fed ( $P < 0.05$ ) conditions compared with controls. Platelet depleted plasma 5-HT concentration positively correlated with colonic activity index under both fasting ( $r = 0.402$ ;  $P = 0.003$ ) and fed ( $r = 0.439$ ;  $P = 0.001$ ) conditions. These data show a possible relationship between endogenous concentrations of 5-HT and sigmoid-colonic motility recorded in both IBS and healthy subjects.

**Keywords** 5-hydroxytryptamine, colonic motility, irritable bowel syndrome.

## INTRODUCTION

Disturbances of large bowel motility have been suggested to be an important feature of the irritable bowel syndrome (IBS). A frequent motor abnormality observed in patients with IBS is an exaggerated sigmoid-colonic motility response to meal ingestion.<sup>1,2</sup> However, this finding has not been reproduced in all studies<sup>3,4</sup> and data from those carried out under fasting conditions is even more variable.<sup>1,5</sup> The lack of reproducibility between studies may be related to both methodological issues<sup>6</sup> and the fact that motility can vary from patient to patient. For instance, some<sup>2,4,7,8</sup> but not all<sup>5</sup> studies have suggested that IBS patients with diarrhoea exhibit increased motility, particularly the number of high amplitude propagating contractions (HAPCs),<sup>2</sup> whilst those with constipation<sup>7</sup> and chronic idiopathic constipation<sup>4,7,8</sup> have reduced motility and less HAPCs compared with healthy controls. Thus the mix of patients studied may significantly influence the overall pattern recorded and has led to much debate as to whether sigmoid-colonic dysmotility is a significant feature of IBS or not.

5-Hydroxytryptamine (5-HT) is thought to play an important role in the normal motor function of the gastrointestinal tract, and depending on the type and location of the receptor subtype it stimulates, can cause either gastrointestinal contraction or relaxation.<sup>9,10</sup> 5-Hydroxytryptamine released from the enterochromaffin (EC) cells of the gastrointestinal tract in response to intraluminal stimuli not only activates intrinsic primary afferent neurons (IPANs) and extrinsic sensory neurons to modulate gastrointestinal function but also enters the circulation to activate distant targets. 5-Hydroxytryptamine found in the blood is almost entirely derived from the EC cells of the gastrointestinal tract<sup>11</sup> and has been shown to increase

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with meal ingestion,<sup>12–15</sup> the magnitude of the response varying depending on meal composition.<sup>12</sup> In patients with IBS, we and others have shown that platelet depleted plasma 5-HT (PDP 5-HT) concentrations are abnormal, with those with diarrhoea (IBS-D) exhibiting elevated concentrations under both fasted and fed conditions, whilst those with constipation (IBS-C) exhibit reduced concentrations under fed conditions compared with healthy controls.<sup>13–15</sup> However, as with colonic motility, the inter-subject variation in PDP 5-HT concentration, especially between IBS patients, and even within subgroups is considerable<sup>13–15</sup> and thus large numbers of subjects are required to show statistical differences between groups. This taken together with the inadequacy of many previous motility studies, in terms of small subject numbers and patient definition, might help to account for some of the current confusion surrounding its role in IBS. Moreover, relating motility to a factor other than bowel habit, such as 5-HT, might improve understanding of the pathophysiological mechanisms associated with this condition.

Therefore, the aim of this study was to assess the potential relationship between PDP 5-HT concentration and sigmoid-colonic motility under both fasting and fed conditions in patients with IBS, independent of bowel habit subtype, and in a group of age and sex matched healthy volunteers.

## MATERIALS AND METHODS

### Subjects

This study was carried out on 35 patients with IBS [18 IBS-D patients (aged 19–42 years; mean age 30 years; five male) and 17 IBS-C patients (23–53 years; 30 years; three male)] and 16 healthy volunteers (aged 18–39 years; 23 years; six male). Irritable bowel syndrome patients with an alternating bowel habit were excluded from the study. Irritable bowel syndrome patients were recruited from the Out Patients Departments of the University Hospitals of South Manchester (tertiary patients excluded), local general practices, advertisement in regional news papers and an existing departmental volunteer pool of patients, and all satisfied the Rome II criteria for IBS and predominant bowel habit sub-type.<sup>16</sup> No subject had co-existent disease and all had normal haematology, biochemistry, urinalysis and sigmoidoscopy, together with a normal colonoscopy or barium enema if aged over 40 years. Age and sex matched healthy volunteers were recruited by advertisement, and all had normal laboratory investigations (as above) and negative toxicology for substances of

abuse. Subjects were excluded if they: had a history of gastrointestinal surgery (other than appendectomy and hiatus hernia repair); had gastrointestinal symptoms related to or exacerbated by consumption of milk or milk products; or were taking drugs that might modify either gastrointestinal function or the 5-HT system, such as analgesic medication, tranquillizers or antidepressants. Female subjects were excluded if they were pregnant, breast feeding or hysterectomized, and all were postpubertal and premenopausal. As there is evidence to suggest that steroid ovarian hormones might affect the 5-HT system<sup>17</sup> all females were studied during the luteal phase of the menstrual cycle (high progesterone and oestrogen) or whilst taking combined (non-phased) oestrogen/progesterone contraceptive medication. All medications and cigarette smoking were stopped for 48 h prior to the study, whilst alcohol and caffeine containing products were prohibited 24 h before the study. All subjects drank below the recommended safe alcohol limit (<21 units week<sup>-1</sup>), smoked <5 cigarettes per day, and had not participated in a clinical trial of any drug within the previous 30 days. Written consent was obtained from all subjects and the study was approved by the South Manchester Medical Research Ethics Committee.

### Study protocol

After an overnight fast, subjects attended the Neurogastroenterology Unit and a solid-state catheter was positioned endoscopically in the sigmoid colon. Following a 60-min rest period, an arm vein was cannulated and 5 mL of blood taken via EDTA vacutainer for baseline fasting concentration of PDP 5-HT. A further 5 mL blood sample was taken 60 min later and followed immediately by the subjects ingesting a standard carbohydrate-rich meal, consisting of 200 g spaghetti (Heinz, Stockley Park, Uxbridge, UK), two medium slices of toast, a jam and fresh cream score (Marks and Spencer, London, UK) and 200 mL water (totalling 65.5 g carbohydrate, 12 g protein, 16 g fat, calorie content of 457 kcal) which was consumed within 10 min.<sup>13,14</sup> Postmeal 5 mL blood samples for PDP 5-HT analysis were taken every 30 min for a further 5 h. Sigmoid-colonic motility was recorded throughout the 60 min pre- and 5 h postmeal periods.

### Measurement of sigmoid-colonic motility

Sigmoid-colonic motility was recorded using a fine (2.7 mm diameter) flexible solid-state catheter incorporating five pressure transducers, spaced 5 cm apart (situated 0, 5, 10, 15 and 20 cm from the distal tip) and

arranged radially around its circumference (Gaeltec Ltd, Isle of Skye, UK).<sup>18,19</sup> The tip of catheter was attached to a colonoscope using biopsy forceps and then introduced into the unprepared bowel to a distance of 35 cm from the anus with minimal air inflation. Care was also taken to ensure that the 35 cm placement of the catheter was accurate and did not reflect stretching of the bowel. Once positioned, the tip of the catheter was released from the forceps and the colonoscope gently withdrawn whilst applying suction to remove any air introduced during the procedure. The catheter was then taped to the gluteal region and the subject positioned in a semi-recumbent position and asked to avoid movement to prevent artifactual fluctuations in intra-abdominal pressure. No sedation was used and no patient complained of undue discomfort during the procedure. The solid-state catheter was connected to a PC computer via an analogue-digital converter (PC-Polygraph; Synectics Medical, Middlesex, UK), and the data stored and analysed using Synectics Medical software (Polygram Lower GI Edition, version 5.0).<sup>18</sup>

### Measurement of platelet depleted plasma concentrations of 5-HT concentrations

The collected blood ( $t = -1$  to 5 h postmeal) was transferred to tubes containing 0.5 mL of 3.12% trisodium citrate and centrifuged (room temperature) twice to ensure no platelet contamination of supernatant; initially at 2500 rpm for 10 min and then at 4000 rpm for a further 10 min.<sup>13,14</sup> Platelet depleted plasma was aspirated and duplicate samples stored at  $-70$  °C for later batch analysis which was carried out blind to subject status. 5-HT concentrations were measured in duplicate using HPLC with fluorimetric detection and the sensitivity of the HPLC system was as previously described.<sup>13,14,20</sup>

### Data and statistical analysis

#### Sigmoid-colonic motility

Using the Synectics Medical automated software (Polygram Lower GI Edition, version 5.0)<sup>18,19</sup> both the pre- and postprandial recording periods were analysed to yield values for (i) the mean number of pressure waves, where a contraction is defined as an increase in pressure  $\geq 20$  mmHg and succeeded by a decrease in pressure of 20 mmHg or more;<sup>18</sup> (ii) the mean amplitude of pressure peaks (mmHg); (iii) the percentage duration of activity calculated as the sum of the duration of individual pressure waves and expressed as a percentage of each

epoch (%) and (iv) the activity index, that is the area under the curve calculated by integration of the curve (mmHg). A detailed explanation of the automated analysis programme has been previously described<sup>18</sup> but in brief, the programme provides values for the above variables every consecutive 10 min epoch for each of the five pressure recording channels.

In addition, the number of contractions (amplitude  $>10$  mmHg) propagating aborally through at least three consecutive channels ( $n$ ) and the number of HAPC<sup>2,21,22</sup> (amplitudes  $>100$  mmHg) propagating aborally through at least three consecutive channels ( $n$ ) were manually calculated by Wendy Atkinson.

For each of the above variables, an overall average was obtained by combining all 10 min epochs pre- and postmeal across all five pressure recording channels. Any major respiratory or movement artefact in the motility recording was excluded from the analysis.

The effect of the meal on colonic motility was assessed by comparing the pre- and postprandial periods using the non-parametric Wilcoxon matched-pairs signed-rank test. A  $P$ -value of  $<0.05$  was taken as significant and data expressed as median and interquartile range unless otherwise stated.

### Platelet depleted plasma 5-HT concentrations

The following end-points were analysed for PDP 5-HT concentrations: (i) fasting concentration, calculated as the average of the preprandial measurements ( $\text{nmol L}^{-1}$ ); (ii) fed concentration, calculated as the average of the postprandial measurements ( $\text{nmol L}^{-1}$ ) and (iii) ratio of average fed to fasting concentrations.

Analysis of covariance models were fitted to the log transformation of the above variables to assess changes and differences between groups. All models were checked for the validity of model assumptions and included terms for subject group and age. In addition, the increase in 5-HT concentration following meal ingestion within each group were analysed using Student's paired  $t$ -test (two-tailed). Correlations between motility and 5-HT concentrations were determined using Spearman's rank (non-parametric data) tests. A  $P$ -value of  $<0.05$  was taken as significant. Data are expressed as adjusted geometric mean and 95% confidence interval unless otherwise stated.

## RESULTS

### Platelet depleted plasma 5-HT concentrations

Platelet depleted plasma 5-HT concentrations were higher under both fasting ( $P < 0.004$ ) and fed

**Table 1** Comparison of platelet depleted plasma 5-hydroxy-tryptamine concentration between patients with IBS and HV

	HV (n = 16)	IBS (n = 35)	Ratio IBS : HV (95%CI)	P-value
Fasting (nmol L <sup>-1</sup> )	12.68	22.65	1.79 (1.22, 2.63)	0.004
Fed (nmol L <sup>-1</sup> )	17.64*	24.59	1.39 (0.96, 2.02)	0.079
Ratio fed : fasted	1.39	1.09	0.78 (0.54, 1.13)	0.187

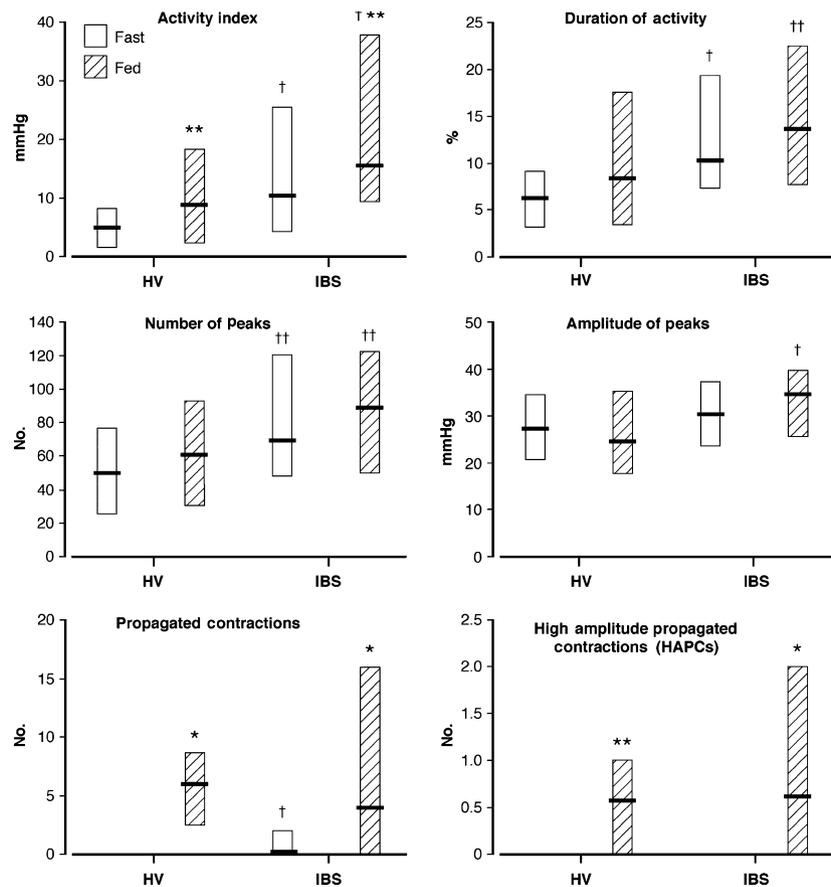
Results expressed as adjusted geometric mean (95% confidence interval). \*P = 0.09 compared with fasting. IBS, irritable bowel syndrome; HV, healthy volunteers.

(P = 0.079) conditions in IBS patients compared with healthy volunteers (Table 1). In addition, PDP 5-HT concentrations were greater under fed than fasting conditions in healthy volunteers (ratio fed : fasting 1.39 (0.24, 1.78); P = 0.09) but not IBS patients (1.09 (0.16, 2.03); P = 0.376) (Table 1). However, the magnitude of the increase in 5-HT concentration with meal ingestion (i.e. the change from fasting to fed) was not

significantly different between the two groups (P = 0.187).

**Sigmoid-colonic motility**

Table 1 shows the various motility parameters measured under both fasted and fed conditions in IBS and healthy subjects. Sigmoid-colonic motility, as measured by activity index was significantly greater in IBS patients under fasting (difference from HV (95% CI): 5.45 mmHg (1.02, 11.73); P = 0.011) and fed (7.36 mmHg (0.74, 15.22); P = 0.028) conditions compared with healthy volunteers (Fig. 1). Under fasting conditions, this was associated with an increased number of contractions (23.31 (-0.68, 49.80); P = 0.062), duration of activity 4.45% [(0.54, 9.41); P = 0.026] and number of propagated contractions [0.24 (0.06, 1.01); P = 0.03] but not amplitude of contractions [2.13 mmHg (-3.13, 7.48); P = 0.516] or number of HAPC [0 (0,0); P = 0.980], whilst under fed conditions, it was associated with increased number of contractions [22.82 (-3.20, 49.38); P = 0.120], amplitude of contractions [6.65 mmHg (0.45, 13.55);



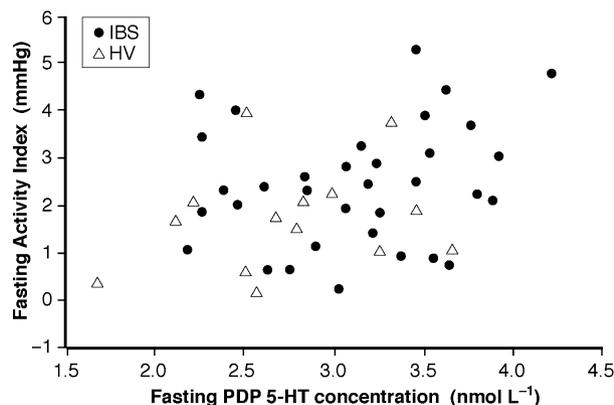
**Figure 1** Comparison of sigmoid-colonic motility parameters between irritable bowel syndrome patients and healthy volunteers under fasting and fed conditions. Data expressed as median (interquartile range). †P < 0.05 compared with controls; ††P ≤ 0.12 compared with controls; \*P < 0.001 compared with fasting; \*\*P < 0.05 compared with fasting.

$P = 0.031$ ], duration of activity [4.42% (-0.56, 9.47);  $P = 0.070$ ] but not the number of propagating contractions [-1.23 (-5.34, 4.41);  $P = 0.667$ ] nor number of HAPC [0.47 (-0.13, 1.01);  $P = 0.465$ ].

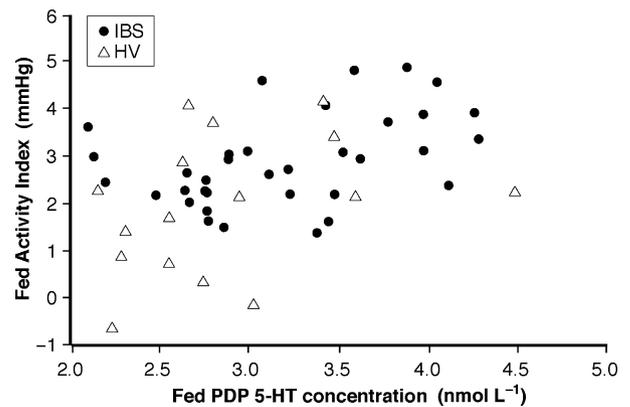
Meal ingestion was associated with a significant increase in activity index (difference from fasting: IBS, 4.08 mmHg (-2.27, 14.45); HV, 2.91 mmHg (-0.80, 8.41);  $P < 0.05$  for both), number of propagating contractions [IBS, 4.29 (0, 13.0); HV, 6.93 (2.5, 8.75)  $P < 0.001$  for both] and HAPC [IBS, 0.69 (0, 2.0);  $P < 0.001$ , HV, 0.64 (0, 1.0);  $P < 0.05$ ] in both IBS patients and healthy controls, although the magnitude of this increase was no different between the two groups. However, there was no significant increase in the amplitude of contractions [IBS, 1.75 mmHg (-3.34, 5.68); HV, -0.58 mmHg (-2.81, 4.87)], duration of activity [IBS, 1.83% (-5.93, 8.76)%; HV, 0.32% (-4.59, 6.90)%] or number of peaks [IBS, 6.36 (0.54, 17.43); HV, 6.47 (0.27, 13.98)].

### Relationship of sigmoid-colonic motility to PDP 5-HT concentrations

Combining both the IBS and healthy subjects, showed that there was a direct correlation between sigmoid-colonic activity index and PDP 5-HT concentration under both fasting ( $r = 0.402$ ;  $P = 0.003$ ) and fed ( $r = 0.439$ ;  $P = 0.001$ ) conditions (Figs 2 and 3). Similar correlations were seen when assessing individually the second ( $r = 0.422$ ;  $P = 0.002$ ), third ( $r = 0.368$ ;  $P = 0.010$ ) and fourth ( $r = 0.327$ ;  $P = 0.024$ ) postprandial hours. Likewise, 5-HT directly correlated with number of peaks (fasted:  $r = 0.352$ ,  $P = 0.011$ ; fed:  $r = 0.322$ ,  $P = 0.021$ ) and showed a tendency to corre-



**Figure 2** Correlation of fasting sigmoid-colonic activity index with platelet depleted plasma 5-hydroxytryptamine concentration in irritable bowel syndrome (IBS) patients and healthy volunteers. Overall  $r = 0.402$ ,  $P = 0.003$ ; IBS patients  $r = 0.170$ ,  $P = 0.329$ ; healthy volunteers  $r = 0.567$ ,  $P = 0.020$ .



**Figure 3** Correlation of fed sigmoid-colonic activity index with platelet depleted plasma 5-hydroxytryptamine concentration in irritable bowel syndrome (IBS) patients and healthy volunteers. Overall  $r = 0.439$ ,  $P = 0.001$ ; IBS patients  $r = 0.435$ ,  $P = 0.009$ ; healthy volunteers  $r = 0.338$ ,  $P = 0.201$ .

late with percentage duration of activity (fasted:  $r = 0.350$ ,  $P = 0.12$ ; fed:  $r = 0.343$ ,  $P = 0.14$ ) but not with amplitude of peaks.

Separating the IBS from healthy subjects, revealed a direct correlation between sigmoid-colonic activity index and PDP 5-HT concentrations under fed ( $r = 0.435$ ;  $P = 0.009$ ) but not fasting conditions ( $r = 0.170$ ;  $P = 0.329$ ) in IBS patients, and under fasting ( $r = 0.567$ ;  $P = 0.020$ ) but not fed ( $r = 0.338$ ;  $P = 0.201$ ) conditions in healthy volunteers (Figs 2 and 3). Others included positive correlations between 5-HT and fasted amplitude of peaks ( $r = 0.286$ ;  $P = 0.096$ ), fed percentage duration of activity ( $r = 0.290$ ,  $P = 0.091$ ), and fasted and fed number of peaks ( $r = 0.231$ ,  $P = 0.183$ ;  $r = 0.283$ ,  $P = 0.103$  respectively) in IBS patients; and fed percentage duration of activity ( $r = 0.405$ ,  $P = 0.120$ ) and fasted number of peaks ( $r = 0.385$ ,  $P = 0.141$ ) in healthy volunteers.

### DISCUSSION

This study has shown for the first time a possible relationship between sigmoid-colonic motility and endogenous levels of 5-HT, as measured by the concentrations found in PDP under fasting and fed conditions in both IBS patients and healthy subjects.

In this evenly mixed cohort of IBS patients with diarrhoea and constipation we found that the concentration of PDP 5-HT was elevated under both fasting and fed conditions compared with healthy volunteers. However, ingestion of the meal was only associated with an increase in PDP 5-HT concentration in the

healthy volunteers, despite this change not being statistically different from that seen in IBS patients. These findings are consistent with the combined data from previous studies showing that IBS-D patients have elevated PDP 5-HT concentrations under both fasting and fed conditions<sup>14</sup> whilst IBS-C patients have reduced fed<sup>14,15</sup> but normal fasting<sup>14</sup> 5-HT concentrations. The fact that IBS-D patients also have a similar<sup>13,14</sup> but IBS-C patients a reduced<sup>14,15</sup> 5-HT meal response (i.e. change in 5-HT concentration from fasting to fed) compared with healthy volunteers probably accounts for the reduced 5-HT meal response seen in this IBS cohort. This observation together with the relatively small numbers of IBS-D and -C patients studied, in whom our previous findings from a much larger number of patients,<sup>14</sup> went undetected, is almost certainly responsible for the lack of statistical difference in 5-HT meal response recorded between IBS and healthy subjects. To have shown differences between IBS-D and -C patients, particularly under fasting conditions would have required approximately twice as many patients as was used in the present study, and carrying out such a large study within a reasonable length of time was beyond the scope of this single centre.

Sigmoid-colonic motility was increased under both fasting and fed conditions in IBS patients compared with healthy volunteers. However the magnitude of the increase in motility (activity index) and the number of high amplitude propagated contractions induced with meal ingestion was similar in both IBS and healthy subjects. Although these observations are in accord with some studies,<sup>1,2,23</sup> inconsistency with others<sup>3-5,7,8,24</sup> may be due to differences in the manometric techniques employed, test meal administered, bowel habit subtype of IBS patients studied and use of bowel preparation prior to placement of the catheter.<sup>6</sup> However, it is of interest that these differences in patterns of motility observed generally reflected the specific concentrations of PDP 5-HT recorded between the IBS and healthy subjects. Indeed sigmoid-colonic activity index positively correlated with the concentration of 5-HT in PDP under both fasted and fed conditions in the subjects as a whole, as did some of other motility parameters (e.g., number of peaks, percentage duration of activity etc) in the group as a whole and in the individual IBS and healthy sub-groups. Our finding that not all motility parameters, such as amplitude or number of peaks correlated with 5-HT probably reflects the fact that these measures are components of the activity index and are therefore less likely to reach statistical significance, especially within the smaller subject sub-groups. Whether the differ-

ences in sigmoid-colonic motility represent the cause or are the consequence of available 5-HT as measured in PDP of IBS and healthy subjects, cannot be determined with certainty. However, the fact that disturbances in gastrointestinal transit tend to be modest in patients with IBS<sup>25</sup> despite the significantly elevated plasma 5-HT concentrations seen under both fasting and fed conditions in IBS-D patients<sup>14</sup> and the significantly limited, and in some instances complete lack of 5-HT response to meal ingestion in IBS-C patients<sup>14,15</sup> would suggest that 5-HT is causing, at least in part the changes in motility rather than vice versa. This is further supported by the recent observations<sup>26</sup> that citalopram, a selective serotonin reuptake inhibitor, which has been shown to also increase plasma 5-HT concentration,<sup>27</sup> increases colonic motility in healthy controls.

Although the present study did not address the mechanism of 5-HT induced sigmoid-colonic motility, the possible involvement of the 5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors in the control of motility is highlighted by the ability of 5-HT<sub>3</sub> receptor antagonists to delay colonic transit<sup>28</sup> and inhibit the colonic motility response to a meal,<sup>29</sup> and 5-HT<sub>4</sub> receptor agonists to accelerate colonic transit<sup>30,31</sup> and increase colonic motility.<sup>32</sup> We have shown an increase in the number of both propagating contractions and HAPC's, and activity index, with meal ingestion in both IBS and healthy subjects. This is consistent with the knowledge that 5-HT released from the EC cells in response to a meal, stimulates IPANs possibly via the 5-HT<sub>4</sub> receptor to augment the peristaltic reflex.<sup>33</sup> The observation that the magnitude of increase in sigmoid-colonic motility was no different between IBS and healthy subjects in this study probably reflects the fact that although the increase in PDP 5-HT concentration with meal ingestion did not reach statistical significance in patients with IBS, there was no significant difference compared with the increase seen in healthy volunteers. 5-HT<sub>3</sub> receptors are widespread in the myenteric plexus but studies in the guinea pig suggest that they rarely mediate responses to endogenous 5-HT,<sup>34</sup> responding only to exogenous 5-HT under normal physiological conditions. This is primarily because SERT and other transporters<sup>35</sup> prevent mucosal 5-HT from reaching the myenteric plexus.<sup>36</sup> However, it could be argued that the increased concentrations seen following meal ingestion in some patients with IBS-D<sup>13,14</sup> might occasionally overflow to the myenteric plexus stimulating 5-HT<sub>3</sub> receptors to cause painful giant migrating contractions.<sup>37,38</sup> Again the lack of difference in both the number of propagating contractions and HAPC stimulated with meal ingestion between IBS and

healthy subjects in the present study is probably related to the fact that there was a similar 5-HT meal response and presence of equal numbers of IBS-D and -C patients in our group, who may have increased and decreased motility, respectively.<sup>2,4,7,8</sup>

Our new observation that there was a positive correlation between PDP 5-HT concentration and sigmoid-colonic motility would suggest that in functional gastrointestinal disorders where reduced motility is an issue, 5-HT modulating agents which increase motility and transit, such as the 5-HT<sub>4</sub> receptor agonists<sup>30–32</sup> would be of benefit, whilst in conditions where increased motility and/or there is a high incidence of HAPCs, agents which reduce motility and delay transit, such as some 5-HT<sub>3</sub> receptor antagonists<sup>28,29</sup> may be helpful, although not all 5-HT<sub>3</sub> receptor antagonist have been shown to have this effect.<sup>39</sup> This would be the case whether the differences in plasma 5-HT concentration are the cause or the result of changes in motility, as it could be speculated that an increase in motility induced by a 5-HT<sub>4</sub> receptor agonist might stimulate the mucosal EC cells to release more 5-HT. Furthermore, it seems reasonable to assume that basing treatment on a clearly and easily measurable factor, such as plasma 5-HT concentration could well be a much more rational approach than simply relying on bowel habit which is often misrepresented.

In conclusion, these data are the first to provide evidence for a possible relationship between endogenous 5-HT and sigmoid-colonic motility in both IBS and healthy subjects and provide additional support for current pharmacological approaches that alter gastrointestinal motility by modulating 5-HT receptors. However, further studies are required to determine whether altered 5-HT causes or is the consequence of altered motility.

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