



HAL
open science

Review Article: The Pathogenesis of Diverticular Disease - Current Perspectives on Motility and Neurotransmitters

Santhini Jeyarajah, Savvas Papagrigroriadis

► **To cite this version:**

Santhini Jeyarajah, Savvas Papagrigroriadis. Review Article: The Pathogenesis of Diverticular Disease - Current Perspectives on Motility and Neurotransmitters. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (7), pp.789. 10.1111/j.1365-2036.2011.04586.x . hal-00614058

HAL Id: hal-00614058

<https://hal.science/hal-00614058>

Submitted on 9 Aug 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Review Article: The Pathogenesis of Diverticular Disease –
Current Perspectives on Motility and Neurotransmitters**

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0461-2010.R2
Wiley - Manuscript type:	Review Article
Date Submitted by the Author:	11-Jan-2011
Complete List of Authors:	Jeyarajah, Santhini; Kings College Hospital, Department of Colorectal Surgery Papagrigoriadis, Savvas; Kings College Hospital, Colorectal Surgery
Keywords:	Diverticular disease < Disease-based, Motility < Topics, Clinical pharmacology < Topics, X keyword = no topic

1
2
3 **Title**
4
5
6
7

8 **Review Article: The Pathogenesis of Diverticular Disease – Current Perspectives on**

9
10 **Motility and Neurotransmitters**
11
12
13
14

15 Authors: Santhini Jeyarajah* & Savvas Papagrigoriadis
16
17
18
19

20 Institution: Department of Colorectal Surgery, Kings College Hospital, London, UK
21
22
23
24

25 *Corresponding Author Details: Department of Colorectal Surgery, Kings College Hospital,
26 London, UK. Email:sanjeyarajah@doctors.net.uk
27
28
29
30
31

32 Running Title: Neurotransmitters and Diverticular Disease
33
34
35
36
37

38 Keywords: Diverticular Disease, Motility, Clinical Pharmacology, Neurotransmitters.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Abstract:

Background: Low fibre diet, structural abnormalities and ageing are traditional aetiological factors implicated in the development of Diverticular Disease (DD). More recently, motility disorders are implicated in its causation leading to speculation that neurotransmitters play a role in mediating these disturbances.

Aims: To draw together studies on the role of neurotransmitters in the development of DD and its symptoms.

Methods: Medline, GoogleScholar and Pubmed were searched for evidence on this subject using the terms neurotransmitters, motility, Diverticular Disease and pathogenesis. Articles relevant to the subject were cited and linked references also reviewed.

Results: Serotonin which has been found to be an excitatory colonic neurotransmitter has been found in early studies to be increased in colonic enterochromaffin cells. Acetylcholine which is thought to be an excitatory neurotransmitter and cholinergic activity has also seen to be increased in DD. These findings may suggest that an increase in excitatory neurotransmitters may result in the hypersegmentation thought to cause pulsion diverticula.

Similarly, a decrease of Nitric Oxide which is inhibitory is found

Conclusions: There is some evidence that neurotransmitters may play a role in the motility disturbances seen in DD however a clear role is yet to be ascertained.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

Although the pathogenesis of Diverticular Disease (DD remains) unclear, it is suggested that it may be a multifactorial disease comprising environmental factors, structural and motility disorders (1, 2). Increasingly neurotransmitters are speculated to underpin the different motility factors leading to the development and symptomatology of this condition. It is suggested that diverticulosis may be attributable to colonic smooth muscle dysfunction that results from vagal attrition associated with aging (3). This may be related to an abnormality in cholinergic activity in smooth muscle is important in the uncomplicated form of the disease with cholinergic denervation hypersensitivity affecting smooth muscle and upregulation of smooth muscle M3 receptors possibly accounting for physiological, and pharmacological abnormalities associated with diverticular disease (4). It is these hypotheses and findings that have contributed to increasing amounts of work being carried out to delineate the role of neurotransmitters in pathogenesis of DD. It is the aim of this review to review the numerous motility and neurotransmitter factors implicated.

Methods

Medline, GoogleScholar and Pubmed were searched for evidence on this subject using the terms search terms: neurotransmitters, motility, Diverticular Disease and pathogenesis up to the year 2009. Articles in English relevant to the subject were cited and linked references were also reviewed.

Traditional Pathogenetic mechanisms in Diverticular Disease

1. Dietary

Traditionally, low fibre diets in western societies have been attributed to the prevalence of this disease in the West (5); (6); (7). Low fibre intake is associated with prolonged colonic transit time, increased water resorption, smaller stool volume, constipation and straining which increases colonic intraluminal pressure, and results in the formation of pulsion diverticula (6, 8). Consistent with this hypothesis, vegetarians have been shown to have significantly higher fiber intake than non vegetarians and a lower prevalence of diverticulosis (9).

a. Diet and Geography

Geography and differences in dietary fibre has long been implicated in the different rates of DD. Prevalence appears to be quite homogenous throughout Europe, without a geographical gradient (10). DD had been found to be 80 times more common in Scotland compared with the native population of Fiji, Singapore and Nigeria and forty times more common in Europeans living in these places likely to be due to their low residue diet (11).

Interestingly however, when people from these areas migrate to high-incidence areas, such as the United States, Europe, and Australia, their rates of diverticular disease increase significantly to match the local population (12). As eluded to previously, in Western countries, diverticula are seen predominantly in the sigmoid and distal descending colon but in the Asian, Africa and Middle Eastern populations diverticular disease occurs almost exclusively in the right colon (13). These racial/ethnic differences in anatomic distribution are probably genetic. When Asians migrate, their diverticulosis occurrence increases, but the anatomic location in the bowel appears to remain unchanged (14).

1
2
3
4
5
6 In a retrospective colonoscopy study in urban London, DD had a lower frequency in migrant
7
8 Indians compared with other ethnic groups. These patients were significantly younger than
9
10 the other age groups however the numbers in this study were small. Here was no difference
11
12 between first and second generation migrants and it is difficult to draw firm conclusions from
13
14 this study (15).
15
16
17
18
19

20 In an endoscopy study of Turkish migrants in the Netherlands, diverticulosis was diagnosed
21
22 significantly more often in migrant men and immigrants with diverticulosis were significantly
23
24 younger than the authentic Dutch. (16). In a population based study in Sweden the risk of
25
26 hospital admission because of diverticular disease, after adjustment for age, sex and socio-
27
28 economic indicators, was lower in non-Western immigrants compared with natives and the
29
30 risk increased with time after the settlement. The overall 10 year cumulative incidence was
31
32 0.44% in men and 0.7% in women and the incidence increased linearly with age. Socio-
33
34 economic status, residency or housing situation were not risk factors which led the authors to
35
36 conclude that diverticular disease appears to be an acquired disorder and acculturation to a
37
38 Western lifestyle has an impact on the risk (17) and a similar cause may be an explanation for
39
40 the other studies cited.
41
42
43
44
45
46
47
48
49

50 2. *Structural pathogenetic factors*

51
52
53
54

55 It has been suggested that a primary abnormality of muscularis propria in DD leading to its
56
57 shortening and thickening, causing it to behave like myostatic contracture might exist and
58
59 was the most consistent feature of diverticular disease (18). Muscle cells retain a normal,
60

1
2
3 non-hypertrophic appearance, and rather, the thickened taenias were due to increased elastin
4 deposition, leading to contraction and secondary thickening of the circular layer (19). The
5
6 consequent plication of the circular layer narrows the lumen, thus increasing the intraluminal
7
8 pressure according to Laplace's law. The resulting hypersegmentation is thought to be
9
10 important in the pathogenesis of the diverticula (20).
11
12
13
14
15
16

17 The muscle abnormality leading to a non-compliant wall seems to be due to mychosis and the
18
19 intrinsic derangement of collagen fibres (21). Mychosis refers to the progressive elastosis of
20
21 the taenia coli attributed to the increased proline in the western diet (19). Abnormalities in
22
23 increased collagen deposition and cross linking are also implicated in decreased colonic
24
25 tensile strength (22, 23).
26
27
28
29
30
31

32 Increased cross-linking of colonic collagen with age and in patients with diverticulosis may
33
34 lead to rigidity and loss of tensile strength (22, 23), an increased synthesis of type III collagen
35
36 may decrease the tensile strength of the circular muscle (24) and collagen fibrils have also
37
38 been seen to be smaller and more tightly packed in the left colon with increasing age and DD
39
40 which may also contribute to the weakness (21).
41
42
43
44
45

46 Along with changes in colonic motility, Arfwidsson et al, noted thickening of both the
47
48 circular muscle layer and taenia of sigmoid diverticular specimens when compared with
49
50 normal controls (25).
51
52
53
54

55 3. Age 56 57 58 59 60

1
2
3 The prevalence of colonic DD is strongly correlated with advancing age. It is relatively
4
5 uncommon before the age of 40 (5%), and increases progressively to as much as 60% in the
6
7 80s and older seen in post mortem and radiological studies (26-29). This may be due to
8
9
10 weakening of the bowel due to aging and reduction in tensile strength of the colon (30, 31).
11

12
13
14
15 Collagen fibrils demonstrate increased crosslinking with age leading to reduced tensile
16
17 strength (32). It has also been demonstrated that the collagen tissue layer between the
18
19 longitudinal and circular layers of smooth muscle of the bowel is reduced by increasing age
20
21 (Pace, 1966). Elastin contents increases throughout life in all layers of the colon which
22
23 contributes to the elastosis seen in DD (26, 33, 34).
24
25
26

27
28
29 There appears to be no clear hereditary pattern to colonic diverticular disease although more
30
31 and more this disease seems to be migrating to younger patients. The incidence varies from
32
33 less than 10% in people younger than 40 years to an estimated 50-80% in patients older than
34
35 80 years (12, 35, 36).
36
37

38
39
40 From an outcome perspective it is this younger age group which is of great clinical interest as
41
42 it is thought to be a more virulent form of the condition. In a study in New Mexico, 6% of
43
44 patients with symptomatic disease were aged 40 years of age or younger (37), in other studies
45
46 the prevalence is even lower representing only 2-5% (38, 39). This younger group has
47
48 disproportionately more men (37) and 25-80% require surgery with a higher chance of
49
50 recurrence in those managed conservatively. (37, 38, 40-43). Similarly in a British hospital
51
52 admission study younger patients were more likely than older patients to undergo an
53
54 operation following admission for diverticular disease. The percentage of admissions with an
55
56 operation decreased with age from 54.2% in the 25-34-year age group to 13.4% in the ≥ 85 -
57
58
59
60

1
2
3 year age group (44). Younger patients are more commonly offered elective surgery which
4
5 may explain this increase (45) (46).
6
7
8
9

10 There is however an increasing awareness of DD in younger patients where previously it was
11 regarded as a disease of the elderly, and where before other diagnoses may be sought to
12 explain symptoms in younger patients, there may be more recognition of DD in this age
13 group (47). The change in this pattern of disease could be due not only to increased
14 awareness but may also reflect cultural and dietary effects previously discussed. Low fibre
15 diet may be more prevalent in this age group resulting in the increased incidence seen.
16
17
18
19
20
21
22
23
24
25
26

27 These traditional aetiological factors are summarised in Table 1.
28
29
30
31

32 **Motility factors in pathogenesis**

33
34
35

36 The commonest motor pattern seen in the colon is tonic segmenting and rhythmic
37 contraction, serving to slow down faecal flow thereby maintaining continence and permitting
38 water absorption and electrolyte exchange. There are also propulsive peristaltic contractions
39 that usually move in the caudal direction that occur on average 6 times a day (48, 49).
40
41
42
43
44
45
46
47

48 The colon has electrical activity in the form of slow waves and fast activity spikes, or action
49 potentials and this activity is implicated in the pathogenesis of DD (50-55).
50
51
52
53
54

55 *1. Pressures*

56
57
58
59
60

1
2
3 Left-sided diverticula which are pulsion pseudo-diverticula, occur most often in the sigmoid
4
5 colon, which has the smallest diameter, lowest compliance and therefore the highest
6
7 intraluminal pressures (56, 57).
8
9

10
11
12 Not only do patients with diverticular disease have higher colonic intraluminal pressures than
13
14 control subjects (58) (25, 50, 59, 60) but it has also been shown that basal and post prandial
15
16 intraluminal pressures are higher in patients with symptomatic DD compared to those with
17
18 asymptomatic DD (61). The motility patterns in DD show similarity to those of Irritable
19
20 Bowel Syndrome (IBS) to the extent that some researchers have suggested that the two
21
22 conditions may be two forms of the same.
23
24
25
26
27

28
29 Painter et al, 1965 used manometry and simultaneous cinematography to claim that
30
31 hypersegmentation led to formation of diverticula and this phenomenon was confirmed by
32
33 more recent studies (14, 62-64)
34
35
36
37

38
39 Colonic transit studies in DD show conflicting results. Diverticular disease patients showed
40
41 delayed colonic transit which was expedited by bran (65). Conversely, another study showed
42
43 faster transit time between caecum and sigmoid colon in patients with DD compared to
44
45 controls but the mean total time of gastrointestinal emptying was no different in either group
46
47 (66). Similarly, Eastwood et al in 1978 found that 60 patients with DD failed to show
48
49 prolonged intestinal transit time, a reduced stool weight or increased intracolonic pressure
50
51 compared to the normal patients (67).
52
53
54
55
56
57
58
59
60

2. *Myoelectrical activity*

Myoelectrical recordings from implanted catheters in the normal colon reveal a combination of slow waves, corresponding to colonic pacemaker activity, and spikes, reflecting muscle contractions. It is believed that the slow waves originate from the interstitial cells of Cajal (68). An early investigation of the myenteric plexus in diverticulosis, found no morphological abnormalities (Vuong et al, 1985). It has been found since that patients with colonic diverticulosis have significantly reduced numbers of colonic ICC and enteric glial cells compared with controls (Bassotti et al, 2005). The consistently significant reduction of all subpopulations of ICC and of enteric glial cells, might explain the colonic motor abnormalities documented in patients with diverticulosis and there may exist an interaction between neurotransmitters and these cellular elements.

In vivo studies have produced contradictory evidence as slow wave activity has been shown to be both unaltered (69, 70) or possibly increased in DD (71-73) Segmental activity is increased in response to cholinergic stimuli (74, 75) in patients with DD. Fast wave activity is increased in patients with DD and these changes have a tendency to persist following resection of the affected segment, suggesting an inherent alteration in electrical activity. However the exact relevance of any myoelectrical changes in relation to mechanical events remains uncertain (59).

Twenty four hour manometry studies showed an overall increase in basal motility of diverticula segments, an abnormal colonic motor response to eating, and a qualitatively and quantitatively abnormal forceful propulsive activity (48).

1
2
3 Other studies have looked at the role of colonic pacemakers. The colon is thought to have at
4
5 least four pacemakers, located at the caecal pole, the caeco-colonic junction, the mid
6
7 transverse colon, and the colo-sigmoid junction (76) . These pacemakers generate slow waves
8
9 (SW) which initiate and govern colonic contractions (51, 53, 54). It has been found that
10
11 "tachyrrhythmic" electrical activity is seen in the early-DD patients who had loose stools or
12
13 constipation and "bradyrhythmic" or "silent" activity with an irregular rhythm and low
14
15 frequency, amplitude, and conduction velocity in the late-DD patients. These patients
16
17 complained of constipation with pellet-like stools. These "dysrhythmias" may result from a
18
19 disordered colonic pacemaker. The resulting colonic spasm seems to result in an intraluminal
20
21 colonic pressure rise.
22
23
24
25
26
27
28

29 3. *Heterogeneity in studies*

30
31
32
33
34 There is conflicting evidence on the role of raised intramural pressure and increased
35
36 myoelectrical activity in DD. The inconsistencies that arise are probably a result of a number
37
38 of factors including methodological differences, heterogeneity of patients and disease states
39
40 compounded by studies with relatively small numbers and differences in anatomical sites of
41
42 investigation.
43
44
45
46
47

48 On these grounds it is difficult to draw a firm conclusion from these investigations although it
49
50 seems reasonable to accept that higher pressures and increased electrical activity are likely to
51
52 be seen in patients with DD but it is unclear whether this a cause or result of the disease.
53
54

55 A Summary of the motility factors implicated in the pathogenesis of DD is presented in Table

56
57
58 2.
59
60

Neurotransmitters and Diverticular Disease

The alterations of colonic motility in DD described above have not been adequately investigated or understood at a molecular level. Our hypothesis is that disorders of neurotransmitters may be responsible for the main motility changes underlying the pathogenesis of DD. In the following section we will try to review some of the known facts about neurotransmitters and the colon and postulate a possible mechanism implicated in DD.

1. Serotonin

Serotonin (5-HT) is 3-(β -aminoethyl)-5-hydroxyindole. It has been found to be the neurotransmitter of a subset of myenteric interneurons, which evoke a slow excitatory postsynaptic response. Seven subtypes of serotonin receptors have been identified, 5-HT₃ and 5-HT₄ receptors are most relevant in gastrointestinal physiology(77).

The gut contains over 95% of the body's 5-HT (78). Enteric neurones synthesize 5-HT and store it. Serotonergic neurons constitute about 2% of all myenteric neurons. The major enteric depot of 5-HT is found in mucosal enterochromaffin cells, which are sensory transducers that utilize 5-HT to activate both intrinsic (via 5-HT_{1P} and 5-HT₄ receptors) and extrinsic (via 5-HT₃ receptors) primary afferent nerves.

The early experiments implicating 5-HT as an enteric neurotransmitter also revealed that enteric 5-HT- containing nerves exhibit the same Na⁺-dependent reuptake mechanism for 5-HT as that utilized by the serotonergic neurones of the central nervous system (CNS) known as SERT on the plasma membrane (79-82). It is inhibited by fluoxetine and by tricyclic

1
2
3 antidepressants. The tricyclic antidepressants display the same order of potency in inhibiting
4
5 enteric and central reuptake of 5-HT.
6
7
8
9

10 When colonic intraluminal pressure increases, enterochromaffin (EC) cells release 5-HT,
11
12 which stimulates vagal and intrinsic (enteric) afferent nerve fibers. As a result, 5-HT plays a
13
14 role in initiating responses as diverse as nausea, vomiting, intestinal secretion, and the
15
16 peristaltic reflex (83-91).
17
18
19

20
21 Serotonin and serotonin binding protein (SBP) (92) is released from the bowel when enteric
22
23 nerves are stimulated electrically or by vagi (93)
24
25
26
27

28
29 5-HT evokes contractions of gut smooth muscle cells, either by stimulating 5-HT₃ receptors
30
31 on nerve cells or 5-HT₂ receptors on muscle (81). Serotonin is also a potent intestinal
32
33 secretagogue as administration of subcutaneous serotonin caused ileal secretion and reduced
34
35 jejunal absorption of water and electrolyte (94), and serotonin also increased serosal to
36
37 mucosal fluxes of chloride in animal models (95).
38
39
40
41

42
43 Neuronal 5-HT₃ receptors are responsible for rapid depolarization responses in myenteric
44
45 neurons, leading to increased release of acetylcholine from cholinergic neurons, facilitating
46
47 the induction of fast excitatory postsynaptic potentials (EPSPs) (96). 5-HT₄ receptors are
48
49 involved in the peristaltic reflex (97-100) A. 5-HT₃ receptors are not just restricted to
50
51 excitatory cholinergic motor nerves; 5-HT₃ receptor activation also releases "inhibitory"
52
53 neurotransmitters in various regions of the gut, leading to smooth muscle relaxation during
54
55 appropriate conditions (101).
56
57
58
59
60

1
2
3 At present, the serotonin receptors with the greatest potential for therapeutic manipulation are
4
5 the 5-HT₃ and 5-HT₄ receptor subtypes.
6
7
8
9

10
11 *a. Action of serotonin and its modulators on the Gastrointestinal tract*

12 *In vivo* studies have shown that serotonin agonists such as prucalopride (5-HT₄ agonist)
13 (102) accelerate colonic motility, whereas serotonin antagonists, especially on 5-HT₃
14
15 receptors (96, 103, 104) inhibit colonic transit or motility leading to the inference that
16
17 serotonin has an excitatory effect on the gut. Serotonin selective reuptake inhibitor (SSRI),
18
19 fluoxetine, which inhibits mucosal 5-HT uptake increases activation of 5-HT (91). The
20
21 secretory action of serotonin is blocked by cisapride (95, 105).
22
23
24
25
26
27

28 Granisetron, a 5-HT₃ antagonist, had no effect on the colonic peristaltic reflex, even though it
29
30 blunted the human gastrocolonic response without altering antral compliance (106).
31
32
33

34
35 *b. Serotonin and its role in GI pathology*

36 Serotonin in IBS has been extensively studied and most information is available in this area.
37
38 Biopsies of patients with IBS had significantly lower mucosal concentrations of serotonin
39
40 than normal controls along with lower concentrations of tryptophan hydroxylase which is a
41
42 rate limiting enzyme in serotonin synthesis (107). In another study, lower serotonin levels
43
44 were observed in mucosal biopsy samples and post prandial blood samples from patients with
45
46 IBS with constipation (IBS-C) than in patients with IBS with diarrhoea (IBS-D) or in healthy
47
48 volunteers (108) (82) with a lower level of SERT mRNA and SERT protein expression in the
49
50 intestinal epithelial cells of IBS patients compared with that of healthy volunteers (107).
51
52
53
54
55
56

57 Systemic review of IBS treatment concluded that there is strong evidence for the
58
59 improvement of global IBS symptoms with two serotonergic agents: the 5-HT₄ selective
60

1
2
3 agonist tegaserod (IBS with constipation) and the 5-HT₃ antagonist alosetron (IBS with
4 diarrhoea). Further data are required for the 5-HT₃ antagonist, cilansetron, and the mixed 5-
5
6 diarrhoea). Further data are required for the 5-HT₃ antagonist, cilansetron, and the mixed 5-
7
8 HT₃antagonist/5-HT₄ agonist renzapride before their utility in IBS can be appraised (109)
9
10 however as IBS is not the focus of this review, this will not be discussed further.
11

12
13 Serotonin has been found to be increased in the colonic mucosa of resected specimens in
14
15 patients with DD (110). This relates to the increased colonic motility seen in DD. Therefore
16
17 serotonin antagonists may have a role in slowing progression of this disease and also
18
19 reducing symptoms, particularly in those patients whose predominant symptom is diarrhoea.
20
21 More directed therapy could also be instituted by carrying out biopsies in patients with DD
22
23 and identifying if there is an increase in serotonin and correlation with symptoms. However a
24
25 more recent study contradicts this finding where no difference has been found between
26
27 serotonin content in normal and Diverticular colonic mucosa (111)
28
29
30
31

32
33 Serotonin which has been found to be an excitatory colonic neurotransmitter has been found
34
35 in early studies to be increased in colonic enterochromaffin cells (Banerjee, 2005). Serotonin
36
37 agonists may therefore may have a role in alleviating the symptoms and possible worsening
38
39 of DD. GABA which is thought to be an inhibitory agent, although not yet clearly identified
40
41 to have a role in DD, may have a converse role to serotonin.
42
43
44
45

46 47 48 2. *Acetylcholine* 49

50
51
52 Acetylcholine is an important neurotransmitter in normal bowel smooth muscle (112) that
53
54 mediates contraction via postsynaptic muscarinic M₃ receptors (113).
55
56
57
58
59
60

1
2
3 In-vitro myoelectric experiments have shown that there is an increase in low frequency and
4 uncoordinated muscle contraction in patients with diverticular disease who have been given
5 exogenous acetylcholine compared with controls (75). It has also been found that activity of
6 choline acetyltransferase was lower in smooth muscle of patients with diverticular disease,
7 M3 receptors have been found to be higher, and sensitivity to exogenous acetylcholine was
8 increased compared to controls. Amplified expression of bowel-muscle M3 receptors could
9 be a compensatory response to a reduction in cholinergic innervation and a mechanism by
10 which smooth-muscle cells increase their sensitivity to acetylcholine, in an attempt to
11 maintain intrinsic background tone (4).
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 This suggests that cholinergic denervation hypersensitivity can affect smooth muscle in DD,
28 and this along with upregulation of smooth muscle M3 receptors might account for specific
29 clinical, physiological, and pharmacological abnormalities associated with diverticular
30 disease including exaggerated post prandial responses and higher than normal colonic
31 motility (114).
32
33
34
35
36
37
38
39
40

41 However, Tomita et al, did not show a significant rise in sensitivity of longitudinal muscle
42 strips to exogenous acetylcholine, despite noting upregulation of M3 receptors in circular and
43 longitudinal muscle (114). As mentioned, diverticular taeniae have been shown by results of
44 immunohistochemical experiments and electron-microscopic analysis, to contain more elastin
45 than controls. Circular muscle elastin content is normal (19). Therefore, despite an
46 upregulation of M3 receptors in longitudinal taeniae, muscle might not express
47 hypersensitivity to exogenous acetylcholine because its contraction is mechanically restricted
48 by the presence of abnormal concentrations of elastin.
49
50
51
52
53
54
55
56
57
58
59
60

3. Nitric oxide

Non-adrenergic non-cholinergic (NANC) inhibitory nerves are important nerves in the enteric nervous system of the human gut. Recently, it has been established that nitric oxide (NO) is released by stimulation of NANC nerves and the NANC inhibitory transmission in the longitudinal muscle of the taenia coli of human colon leads to colonic relaxation (113, 115).

NO has also be found to stimulate basal acetylcholine release from myenteric neurones through activation of guanylyl cyclase and inhibits the depolarization evoked release of acetylcholine by a presynaptic mechanism unrelated to cyclic GMP by pro-contractile cholinergic nerves implying that NO is not only an inhibitory transmitter to intestinal smooth muscles through NANC but also a modulator of cholinergic neurotransmission in the myenteric plexus (116). Nitroergic neurones project to both circular and longitudinal muscles (112, 117) and are important mediators of resting colonic smooth muscle tone (118)

It has been found that the diverticular colon was more strongly innervated by cholinergic nerves than the normal colon and NANC inhibitory nerves were found to act on the normal colon and to a lesser extent in the diverticular colon. There is also reduction of nitric oxide mediation on the relaxation reaction of NANC nerves in the normal colon compared to in the diverticular colon. This suggested that diminution of action of non-adrenergic non-cholinergic inhibitory nerves and substances such as nitric oxide may result in the high intraluminal pressure caused by colonic segmentation observed in the left-sided colon with diverticula (119). This was also found to be true for right and left sided diverticular (114, 119)

Most recently uncomplicated diverticular longitudinal muscle has been shown to have lower nitric oxide immunoreactivity compared with controls and increased elastosis. This lowered

1
2
3 nitric oxide quantity again led to the postulation that decreased relaxation in the colon and
4
5 uncoordinated peristaltic activity leading to “closed hypersegmentation” and the high
6
7
8 pressure generated may lead to the formation of diverticula (120)
9

10 11 12 13 4. *Neuropeptides* 14 15

16
17 Vasoactive Intestinal Polypeptide (VIP) containing nerve cells in the myenteric plexus have
18
19 been shown to project to the circular muscle, the submucous plexus and other cell bodies
20
21 within the myenteric plexus (121). It is known that VIP has an inhibitory role in peristalsis
22
23 (122-125).
24
25

26
27
28 An abnormally low concentration of VIP in all the colon wall except mucosa, circular muscle
29
30 and taenia has been shown in idiopathic constipation and would possibly correlate to excess
31
32 segmenting and reduced propulsion (126, 127). Conversely, in diverticular disease, the VIP
33
34 content of the mucosa and whole wall minus the mucosal layer was increased when compared
35
36 with control tissue but was unaltered in the circular muscle and taenia coli. Substance P and
37
38 neuropeptide Y levels in all layers of colonic wall were unaltered in these two diseases. The
39
40 disturbances in the normal neural content of VIP in the bowel wall in idiopathic constipation
41
42 and diverticular disease may initiate or contribute to the functional changes seen in these
43
44
45 disorders (127).
46
47
48
49

50
51 Substance P is the main neurotransmitter after Acetylcholine for excitatory motor neurones.
52
53 Other than the above study however, little is known about its role in Diverticular Disease
54
55 (128). Similar to Ach however, it may be shown to be have attenuated activity in this
56
57
58 condition.
59
60

1
2
3 A summary of these neurotransmitters and their actions in the pathogenesis of DD is
4
5 presented in Table 3.
6
7
8
9

10 11 **The interplay between pathogenesis and neurotransmitters**

12
13 As mentioned in the pathogenesis section, motility of colon in DD is abnormal. The effects
14
15 seen as reported in the literature vary however it can generally be surmised that intraluminal
16
17 pressures are likely to be increased both basally and post prandially, (14, 25, 50, 58, 60, 64).
18
19 This was also seen in right sided DD (129).
20
21
22
23

24
25 Serotonin which has been found to be an excitatory colonic neurotransmitter has been found
26
27 in early studies to be increased in colonic enterochromaffin cells (110). Serotonin agonists
28
29 may therefore may have a role in alleviating the symptoms and possible worsening of DD.
30
31
32
33

34
35 Acetylcholine which is thought to be an excitatory neurotransmitter and cholinergic activity
36
37 has also seen to be increased in DD may again have a role. These findings may suggest that
38
39 an increase in excitatory neurotransmitters may result in the hypersegmentation thought to the
40
41 cause of pulsion diverticula. Similarly, a decrease of Nitric Oxide which is inhibitory is
42
43 found.
44
45
46
47
48

49
50 Conversely, Vasoactive intestinal polypeptide which is inhibitory is found to be increased
51
52 and may related to formation of pulsion diverticula due to slow transit and constipation
53
54 however there is no clear evidence of this at present.
55

56
57 The interactions between these neurotransmitters and their subsequent effect on colonic
58
59 motility and pathogenesis in DD is presented in Figure 1.
60

Conclusions

These neurotransmitter studies number in single reports, **having not been reproduced, usually carrying only small sample sizes** and a great deal more work is required to clearly delineate the role of neurotransmitters in the pathogenesis of DD particularly in *in vivo human studies*. As far as therapeutic **interventions are** concerned for control and disease progression control, there may be roles for 5-HT4 selective agonists tegaserod and the 5-HT3 antagonists depending on symptoms, similar to **their potential use** in IBS. M3 receptor antagonists and Nitric oxide agonists which encourage relaxation may also have a role. For VIP however, the current data **are contradictory**.

Tables & Figures

Table 1: Summary of traditional aetiological factors implicated in DD

Factor	Anomaly
Diet	Decreased Fibre
Structural	Abnormality of muscularis propria in the form of mychosis
Ageing	Weakening of bowel wall due to decreased cross linking and deposition of collagen fibres and increased elastosis

Table 2: Summary of Motility Changes implicated in the pathogenesis of DD

Motility Factors	Changes Seen
Pressures	<ul style="list-style-type: none"> Increased intraluminal pressures demonstrated in DD colon Hypersegmentation
Colonic transit	<ul style="list-style-type: none"> Conflicting results
Myoelectrical activity	<ul style="list-style-type: none"> Increased and unaltered slow wave activity had been found the relevance of which is uncertain

	<ul style="list-style-type: none">• Increased basal motility• Decreased frequency of mass movements and increased segmental activity in aging leading to hypersegmentation.• Disordered “colonic pacemaker” activity leading to increased activity in early DD and slower activity in late DD.
--	--

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

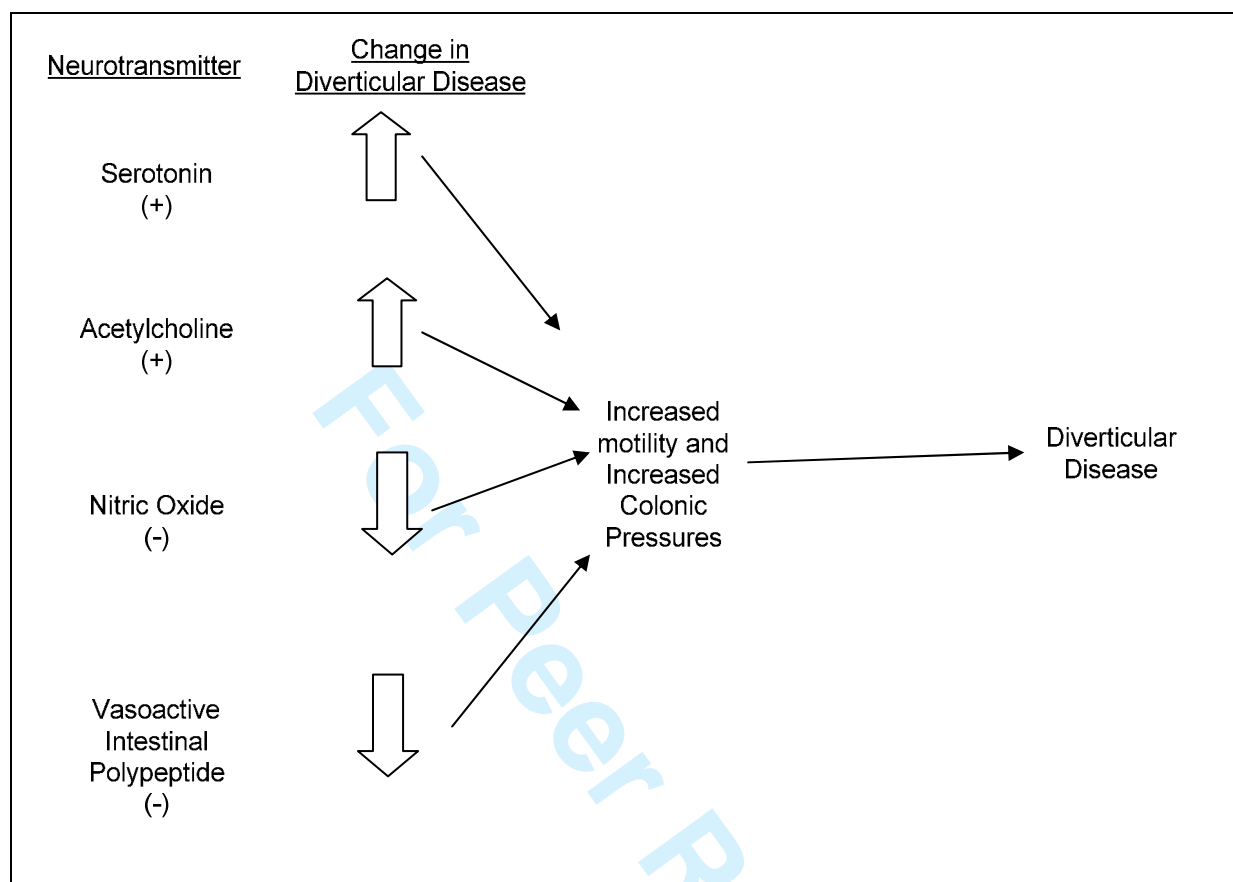
Table 3: Summary of characteristics and actions of neurotransmitters on the colon and the implications in Diverticular Disease

Neurotransmitter	Characteristics & Actions	Role in GI pathology	Avenues for further research
SEROTONIN	<p>Found in colonic mucosal enterochromaffin cells acting via 5-HT₃ and 4 receptors with SERT, a mucosal Na⁺ dependent reuptake mechanism</p> <p>Increased colonic intraluminal pressure leads to 5-HT release from enterochromaffin cells resulting in:</p> <ul style="list-style-type: none"> • increased contraction of smooth muscle cells • intestinal ileal secretion and lack of jejunal absorption • evokes fast excitatory post-synaptic potentials <p>Serotonin agonists accelerates colonic motility and antagonists inhibit colonic motility</p>	<p>IBS</p> <ul style="list-style-type: none"> • Decreased mucosal and post prandial release in IBS-Constipation <p>DD</p> <ul style="list-style-type: none"> • Increased serotonin in enterochromaffin cells of DD resected colons 	<p>Increased DD studies to further clarify the role of serotonin including the action of 5-HT modulation on the clinical syndrome</p>
ACETYLCHOLINE	<p>Well defined role in increasing bowel smooth muscle via post-synaptic muscarinic M₃ receptors</p>	<p>DD</p> <ul style="list-style-type: none"> • Decreased density in old age 	<p>Therapeutic modulation of Ach</p>

		<ul style="list-style-type: none"> Increased low frequency uncoordinated muscle contraction when stimulated by exogenous Ach Increased number and sensitivity of M3 receptors 	
NITROUS OXIDE	<ul style="list-style-type: none"> NO released by NANC inhibitory nerves in the myenteric plexus leading to colonic relaxation NO also modulates Ach through guanylyl cyclase and c-GMP 	DD <ul style="list-style-type: none"> Decreased activity of NANC Decreased NO mediation on NANC 	Increased clarity on the role of NO in colon and other GI pathology
VASOACTIVE INTESTINAL POLYPEPTIDE	<ul style="list-style-type: none"> Found in the myenteric plexus Appears to have an inhibitory role in peristalsis 	Idiopathic Constipation <ul style="list-style-type: none"> Decreased concentration of VIP resulting in hypersegmentation and propulsion DD <ul style="list-style-type: none"> Increased VIP seen in myenteric plexus of DD colon 	Increased clarity on the role of VIP and other neuropeptides in the human colon and in GI pathology

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Figure 1: Interactions between colonic neurotransmitters and implications on the

Pathogenesis of DD

(+) excitatory

(-) inhibitory

References

1. Simpson J, Spiller R. Colonic diverticular disease. *Clin Evid.* 2002 Dec(8):436-44.
2. M J Ford MCAJAW. Differences in colonic tone and phasic response to a meal in the transverse and sigmoid human colon. *Gut* 1995;37:264-9.
3. Yun AJ, Bazar KA, Lee PY. A new mechanism for diverticular diseases: aging-related vagal withdrawal. *Med Hypotheses.* 2005;64(2):252-5.
4. Golder M, Burleigh DE, Belai A, Ghali L, Ashby D, Lunniss PJ, et al. Smooth muscle cholinergic denervation hypersensitivity in diverticular disease. *Lancet.* 2003 Jun 7;361(9373):1945-51.
5. Painter NS, Burkitt DP. Diverticular disease of the colon: a deficiency disease of Western civilization. *Br Med J.* 1971 May 22;2(759):450-4.
6. Burkitt D. Diverticular disease of the colon epidemiological evidence relating it to fibre-depleted diets. *Trans Med Soc Lond.* 1973;89:81-4.
7. Painter NS, Burkitt DP. Diverticular disease of the colon, a 20th century problem. *Clin Gastroenterol.* 1975 Jan;4(1):3-21.
8. Burkitt DP WA, Painter NS. Effect of dietary fibre on stools and transit-times and its role in the causation of disease. *Lancet.* 1979;2:1408 - 11.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
9. Gear JS, Ware AC, Nolan DJ, Fursdon PS, Brodribb AJ, Mann JI. Dietary fibre and asymptomatic diverticular disease of the colon. *Proc Nutr Soc.* 1978 May;37(1):13A.
10. Delvaux M. Diverticular disease of the colon in Europe: epidemiology, impact on citizen health and prevention. *Aliment Pharmacol Ther.* 2003 Nov;18 Suppl 3:71-4.
11. J Kyle AA, L Tinckler and J. deBeaux. . Incidence of diverticulitis. *Scand J Gastroenterol.* 1967; 2:77-80.
12. Stollman NR, JB. . Diverticular disease NJ: Slack, Inc; 2002.
13. Schoetz DJ, Jr. Diverticular disease of the colon: a century-old problem. *Dis Colon Rectum.* 1999 Jun;42(6):703-9.
14. Mimura T, Emanuel A, Kamm MA. Pathophysiology of diverticular disease. *Best Pract Res Clin Gastroenterol.* 2002 Aug;16(4):563-76.
15. Kang JY, Dhar A, Pollok R, Leicester RJ, Benson MJ, Kumar D, et al. Diverticular disease of the colon: ethnic differences in frequency. *Aliment Pharmacol Ther.* 2004 Apr 1;19(7):765-9.
16. Loffeld RJ. Diverticulosis of the colon is rare amongst immigrants living in the Zaanstreek region in the Netherlands. *Colorectal Dis.* 2005 Nov;7(6):559-62.
17. Hjern F, Johansson C, Mellgren A, Baxter NN, Hjern A. Diverticular disease and migration--the influence of acculturation to a Western lifestyle on diverticular disease. *Aliment Pharmacol Ther.* 2006 Mar 15;23(6):797-805.
18. Morson BC. The Muscle Abnormality in Diverticular Disease of the Colon. *Proc R Soc Med.* 1963 Sep;56:798-800.
19. Whiteway J, Morson BC. Elastosis in diverticular disease of the sigmoid colon. *Gut.* 1985 Mar;26(3):258-66.
20. Painter NS. Diverticular disease of the colon--a disease of the century. *Lancet.* 1969 Sep 13;2(7620):586-8.
21. Thomson HJ, Busuttill A, Eastwood MA, Smith AN, Elton RA. Submucosal collagen changes in the normal colon and in diverticular disease. *Int J Colorectal Dis.* 1987 Nov;2(4):208-13.
22. Wess L EM, Edwards CA, Busuttill A, Miller A. Collagen alteration in an animal model of colonic diverticulosis. *Gut.* 1996;38:701-06.
23. Wess L EM, Wess TJ, Busuttill A, Miller A. Cross linking of collagen is increased in colonic diverticulosis. *Gut* 1995; 37:91-4.
24. Bode MK KT, Makela J, Risteli L, Risteli J. Type I and III collagens in human colon cancer and diverticulosis. *Scand J Gastroenterol* 2000;35:747-52.
25. Arfwidsson S, Knock NG, Lehmann L, Winberg T. Pathogenesis of Multiple Diverticula of the Sigmoid Colon in Diverticular Disease. *Acta Chir Scand Suppl.* 1964;63:SUPPL 342:1-68.
26. Parks TG, Connell AM. Motility studies in diverticular disease of the colon. *Gut.* 1969 Jul;10(7):534-42.
27. Parks TG. Natural history of diverticular disease of the colon. *Clin Gastroenterol.* 1975 Jan;4(1):53-69.
28. Hughes LE. Postmortem survey of diverticular disease of the colon. II. The muscular abnormality of the sigmoid colon. *Gut.* 1969 May;10(5):344-51.
29. Gear JS, Ware A, Fursdon P, Mann JI, Nolan DJ, Brodribb AJ, et al. Symptomless diverticular disease and intake of dietary fibre. *Lancet.* 1979 Mar 10;1(8115):511-4.
30. Iwasaki T OT. Study on the strength of human intestinal walls. *Journal of the Kyoto Prefectural University of Medicine* 1953;52:673-702.

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
31. Watters DA, Smith AN, Eastwood MA, Anderson KC, Elton RA, Mugerwa JW. Mechanical properties of the colon: comparison of the features of the African and European colon in vitro. *Gut*. 1985 Apr;26(4):384-92.
32. Wess L EM, Wess TJ, Busuttil A, Miller A. Cross linking of collagen is increased in colonic diverticulosis. *Gut*. 1995; 37:91-4.
33. Smith AN. Colonic muscle in diverticular disease. *Clin Gastroenterol*. 1986 Oct;15(4):917-35.
34. Smith AN, Shepherd J. Proceedings: The strength of the colon wall in diverticular disease. *Br J Surg*. 1976 Aug;63(8):666.
35. Wolff BG, Devine RM. Surgical management of diverticulitis. *Am Surg*. 2000 Feb;66(2):153-6.
36. Marinella MA, Mustafa M. Acute diverticulitis in patients 40 years of age and younger. *Am J Emerg Med*. 2000 Mar;18(2):140-2.
37. Acosta JA, Grebenc ML, Doberneck RC, McCarthy JD, Fry DE. Colonic diverticular disease in patients 40 years old or younger. *Am Surg*. 1992 Oct;58(10):605-7.
38. Roberts PL, Veidenheimer MC. Current management of diverticulitis. *Adv Surg*. 1994;27:189-208.
39. Parks TG. Natural history of diverticular disease of the colon. A review of 521 cases. *Br Med J*. 1969 Dec 13;4(684):639-42.
40. Konvolinka CW. Acute diverticulitis under age forty. *Am J Surg*. 1994 Jun;167(6):562-5.
41. Freischlag J, Bennion RS, Thompson JE, Jr. Complications of diverticular disease of the colon in young people. *Dis Colon Rectum*. 1986 Oct;29(10):639-43.
42. Vignati PV, Welch JP, Cohen JL. Long-term management of diverticulitis in young patients. *Dis Colon Rectum*. 1995 Jun;38(6):627-9.
43. Spivak H, Weinrauch S, Harvey JC, Surick B, Ferstenberg H, Friedman I. Acute colonic diverticulitis in the young. *Dis Colon Rectum*. 1997 May;40(5):570-4.
44. Kang JY, Hoare J, Tinto A, Subramanian S, Ellis C, Majeed A, et al. Diverticular disease of the colon--on the rise: a study of hospital admissions in England between 1989/1990 and 1999/2000. *Aliment Pharmacol Ther*. 2003 May 1;17(9):1189-95.
45. Etzioni DA, Cannom RR, Ault GT, Beart RW, Jr., Kaiser AM. Diverticulitis in California from 1995 to 2006: increased rates of treatment for younger patients. *Am Surg*. 2009 Oct;75(10):981-5.
46. Boudart C, Simoens C, Thill V, Debergh N, Smets D, Mendes da Costa P. Management of sigmoid diverticulitis: a retrospective study of 268 patients. *Hepatogastroenterology*. 2008 Nov-Dec;55(88):2065-71.
47. Janes S, Meagher A, Faragher IG, Shedda S, Frizelle FA. The place of elective surgery following acute diverticulitis in young patients: when is surgery indicated? An analysis of the literature. *Dis Colon Rectum*. 2009 May;52(5):1008-16.
48. Bassotti G, Battaglia E, Spinozzi F, Pelli MA, Tonini M. Twenty-four hour recordings of colonic motility in patients with diverticular disease: evidence for abnormal motility and propulsive activity. *Dis Colon Rectum*. 2001 Dec;44(12):1814-20.
49. Bassotti G, Battaglia E, De Roberto G, Morelli A, Tonini M, Villanacci V. Alterations in colonic motility and relationship to pain in colonic diverticulosis. *Clin Gastroenterol Hepatol*. 2005 Mar;3(3):248-53.
50. Shafik A, Ahmed I, Shafik AA, El Sibai O. Diverticular disease: electrophysiologic study and a new concept of pathogenesis. *World J Surg*. 2004 Apr;28(4):411-5.
51. Quigley EM, Phillips SF, Dent J, Taylor BM. Myoelectric activity and intraluminal pressure of the canine ileocolonic sphincter. *Gastroenterology*. 1983 Nov;85(5):1054-62.

- 1
- 2
- 3
- 4 52. Durdle NG, Kingma YJ, Bowes KL, Chambers MM. Origin of slow waves in the
- 5 gastroenterology. 1983 Feb;84(2):375-82.
- 6 53. Bueno L, Fioramonti J, Ruckebusch Y, Frexinos J, Coulom P. Evaluation of colonic
- 7 myoelectrical activity in health and functional disorders. Gut. 1980 Jun;21(6):480-5.
- 8 54. Shafik A. Sigmoido-rectal junction reflex: role in the defecation mechanism. Clin
- 9 Anat. 1996;9(6):391-4.
- 10 55. Shafik A. The hypertonic rectosigmoid junction: description of a new
- 11 clinicopathologic entity causing constipation. Surg Laparosc Endosc. 1997 Apr;7(2):116-20.
- 12 56. Waldron DJ, Gill RC, Bowes KL. Pressure response of human colon to intraluminal
- 13 distension. Dig Dis Sci. 1989 Aug;34(8):1163-7.
- 14 57. Ford MJ, Camilleri M, Wiste JA, Hanson RB. Differences in colonic tone and phasic
- 15 response to a meal in the transverse and sigmoid human colon. Gut. 1995 Aug;37(2):264-9.
- 16 58. Painter NS, Truelove SC. The Intraluminal Pressure Patterns in Diverticulosis of the
- 17 Colon. I. Resting Patterns of Pressure. Ii. the Effect of Morphine. Gut. 1964 Jun;5:201-13.
- 18 59. Parks TG. Motor responses in unresected and resected diverticular disease of the
- 19 colon. Proc R Soc Med. 1970;63 Suppl:3-6.
- 20 60. Trotman IF, Misiewicz JJ. Sigmoid motility in diverticular disease and the irritable
- 21 bowel syndrome. Gut. 1988 Feb;29(2):218-22.
- 22 61. Cortesini C, Pantalone D. Usefulness of colonic motility study in identifying patients
- 23 at risk for complicated diverticular disease. Dis Colon Rectum. 1991 Apr;34(4):339-42.
- 24 62. Brodribb AJ, Humphreys DM. Diverticular disease: three studies. Part I--Relation to
- 25 other disorders and fibre intake. Br Med J. 1976 Feb 21;1(6007):424-5.
- 26 63. Painter NS, Truelove SC, Ardran GM, Tuckey M. Segmentation and the Localization
- 27 of Intraluminal Pressures in the Human Colon, with Special Reference to the Pathogenesis of
- 28 Colonic Diverticula. Gastroenterology. 1965 Aug;49:169-77.
- 29 64. Painter NS. The cause of diverticular disease of the colon, its symptoms and its
- 30 complications. Review and hypothesis. J R Coll Surg Edinb. 1985 Apr;30(2):118-22.
- 31 65. Kirwan WO, Smith AN. Colonic propulsion in diverticular disease, idiopathic
- 32 constipation, and the irritable colon syndrome. Scand J Gastroenterol. 1977;12(3):331-5.
- 33 66. Leandro PA, Ceconello I, Habr-Gama A, de Oliveireira e Silva A, Pontes JF.
- 34 Gastrointestinal motility in normal subjects and patients with diverticulosis of the colon. Arq
- 35 Gastroenterol. 1984 Oct-Dec;21(4):157-63.
- 36 67. Eastwood MA, Smith AN, Brydon WG, Pritchard J. Colonic function in patients with
- 37 diverticular disease. Lancet. 1978 Jun 3;1(8075):1181-2.
- 38 68. Sanders KM. A case for interstitial cells of Cajal as pacemakers and mediators of
- 39 neurotransmission in the gastrointestinal tract. Gastroenterology. 1996 Aug;111(2):492-515.
- 40 69. Suchowiecky M, Clarke DD, Bhasker M, Perry RJ, Snape WJ, Jr. Effect of secoverine
- 41 on colonic myoelectric activity in diverticular disease of the colon. Dig Dis Sci. 1987
- 42 Aug;32(8):833-40.
- 43 70. Katschinski M, Lederer P, Ellermann A, Ganzleben R, Lux G, Arnold R. Myoelectric
- 44 and manometric patterns of human rectosigmoid colon in irritable bowel syndrome and
- 45 diverticulosis. Scand J Gastroenterol. 1990 Jul;25(7):761-8.
- 46 71. Taylor I, Duthie HL. Bran tablets and diverticular disease. Br Med J. 1976 Apr
- 47 24;1(6016):988-90.
- 48 72. Flynn M, Hyland J, Hammond P, Darby C, Taylor I. Faecal bile acid excretion in
- 49 diverticular disease. Br J Surg. 1980 Sep;67(9):629-32.
- 50 73. Hyland JM, Darby CF, Hammond P, Taylor I. Myoelectrical activity of the sigmoid
- 51 colon in patients with diverticular disease and the irritable colon syndrome suffering from
- 52 diarrhoea. Digestion. 1980;20(5):293-9.
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
- 2
- 3
- 4 74. Huizinga JD. Electrophysiology of human colon motility in health and disease. *Clin Gastroenterol.* 1986 Oct;15(4):879-901.
- 5
- 6 75. Huizinga JD, Waterfall WE, Stern HS. Abnormal response to cholinergic stimulation
- 7 in the circular muscle layer of the human colon in diverticular disease. *Scand J Gastroenterol.*
- 8 1999 Jul;34(7):683-8.
- 9 76. Shafik A, El-Sibai O, Shafik AA. Electrophysiologic identification of the location of
- 10 the colonic pacemakers. A human study. *Front Biosci.* 2002 Feb 1;7:b1-5.
- 11 77. Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, et al.
- 12 Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable
- 13 bowel syndrome. *Gastroenterology.* 2002 Aug;123(2):425-32.
- 14 78. Gershon MD, Dreyfus CF, Pickel VM, Joh TH, Reis DJ. Serotonergic neurons in the
- 15 peripheral nervous system: identification in gut by immunohistochemical localization of
- 16 tryptophan hydroxylase. *Proc Natl Acad Sci U S A.* 1977 Jul;74(7):3086-9.
- 17 79. Robinson RG, Gershon MD. Synthesis and uptake of 5-hydroxytryptamine by the
- 18 myenteric plexus of the guinea-pig ileum. A histochemical study. *J Pharmacol Exp Ther.*
- 19 1971 Aug;178(2):311-24.
- 20 80. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on
- 21 irritable bowel syndrome. *Gastroenterology.* 2002 Dec;123(6):2108-31.
- 22 81. Richardson BP, Engel G, Donatsch P, Stadler PA. Identification of serotonin M-
- 23 receptor subtypes and their specific blockade by a new class of drugs. *Nature.* 1985 Jul 11-
- 24 17;316(6024):126-31.
- 25 82. Bearcroft CP, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in
- 26 diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut.* 1998 Jan;42(1):42-6.
- 27 83. Bulbring E, Crema A. The release of 5-hydroxytryptamine in relation to pressure
- 28 exerted on the intestinal mucosa. *J Physiol.* 1959 Apr 23;146(1):18-28.
- 29 84. Bulbring E, Crema A. Observations concerning the action of 5-hydroxytryptamine on
- 30 the peristaltic reflex. *Br J Pharmacol Chemother.* 1958 Dec;13(4):444-57.
- 31 85. Bulbring E, Lin RC. The effect of intraluminal application of 5-hydroxytryptamine
- 32 and 5-hydroxytryptophan on peristalsis; the local production of 5-HT and its release in
- 33 relation to intraluminal pressure and propulsive activity. *J Physiol.* 1958 Mar 11;140(3):381-
- 34 407.
- 35 86. Sidhu M, Cooke HJ. Role for 5-HT and ACh in submucosal reflexes mediating
- 36 colonic secretion. *Am J Physiol.* 1995 Sep;269(3 Pt 1):G346-51.
- 37 87. Kirchgessner AL, Tamir H, Gershon MD. Identification and stimulation by serotonin
- 38 of intrinsic sensory neurons of the submucosal plexus of the guinea pig gut: activity-induced
- 39 expression of Fos immunoreactivity. *J Neurosci.* 1992 Jan;12(1):235-48.
- 40 88. Kirchgessner AL, Liu MT, Raymond JR, Gershon MD. Identification of cells that
- 41 express 5-hydroxytryptamine1A receptors in the nervous systems of the bowel and pancreas.
- 42 *J Comp Neurol.* 1996 Jan 15;364(3):439-55.
- 43 89. Blackshaw LA, Grundy D. Effects of 5-hydroxytryptamine on discharge of vagal
- 44 mucosal afferent fibres from the upper gastrointestinal tract of the ferret. *J Auton Nerv Syst.*
- 45 1993 Oct;45(1):41-50.
- 46 90. Hillsley K, Kirkup AJ, Grundy D. Direct and indirect actions of 5-hydroxytryptamine
- 47 on the discharge of mesenteric afferent fibres innervating the rat jejunum. *J Physiol.* 1998 Jan
- 48 15;506 (Pt 2):551-61.
- 49 91. Chen JX, Pan H, Rothman TP, Wade PR, Gershon MD. Guinea pig 5-HT transporter:
- 50 cloning, expression, distribution, and function in intestinal sensory reception. *Am J Physiol.*
- 51 1998 Sep;275(3 Pt 1):G433-48.
- 52 92. Jonakait GM, Tamir H, Gintzler AR, Gershon MD. Release of [3H]serotonin and its
- 53 binding protein from enteric neurons. *Brain Res.* 1979 Sep 28;174(1):55-69.
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
- 2
- 3
- 4 93. Gershon MD, Tamir H. Release of endogenous 5-hydroxytryptamine from resting and
- 5 stimulated enteric neurons. *Neuroscience*. 1981;6(11):2277-86.
- 6 94. Donowitz M, Charney AN, Heffernan JM. Effect of serotonin treatment on intestinal
- 7 transport in the rabbit. *Am J Physiol*. 1977 Jan;232(1):E85-94.
- 8 95. Siriwardena A, Kellum JM, Jr. A 5-HT₂ receptor mediates serotonin-induced
- 9 electrolyte transport in rat left colon. *J Surg Res*. 1993 Sep;55(3):323-9.
- 10 96. Gershon MD. Review article: roles played by 5-hydroxytryptamine in the physiology
- 11 of the bowel. *Aliment Pharmacol Ther*. 1999 May;13 Suppl 2:15-30.
- 12 97. Foxx-Orenstein AE, Kuemmerle JF, Grider JR. Distinct 5-HT receptors mediate the
- 13 peristaltic reflex induced by mucosal stimuli in human and guinea pig intestine.
- 14 *Gastroenterology*. 1996 Nov;111(5):1281-90.
- 15 98. Kadowaki M, Wade PR, Gershon MD. Participation of 5-HT₃, 5-HT₄, and nicotinic
- 16 receptors in the peristaltic reflex of guinea pig distal colon. *Am J Physiol*. 1996 Nov;271(5 Pt
- 17 1):G849-57.
- 18 99. Tuladhar BR, Costall B, Naylor RJ. Pharmacological characterization of the 5-
- 19 hydroxytryptamine receptor mediating relaxation in the rat isolated ileum. *Br J Pharmacol*.
- 20 1996 Sep;119(2):303-10.
- 21 100. Tuladhar BR, Kaisar M, Naylor RJ. Evidence for a 5-HT₃ receptor involvement in the
- 22 facilitation of peristalsis on mucosal application of 5-HT in the guinea pig isolated ileum. *Br*
- 23 *J Pharmacol*. 1997 Nov;122(6):1174-8.
- 24 101. Drakontides AB, Gershon MD. 5-hydroxytryptamine receptors in the mouse
- 25 duodenum. *Br J Pharmacol Chemother*. 1968 Jul;33(3):480-92.
- 26 102. Bouras EP, Camilleri M, Burton DD, Thomforde G, McKinzie S, Zinsmeister AR.
- 27 Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation
- 28 without a rectal evacuation disorder. *Gastroenterology*. 2001 Feb;120(2):354-60.
- 29 103. Kadowaki M, Nagakura Y, Tomoi M, Mori J, Kohsaka M. Effect of FK1052, a potent
- 30 5-hydroxytryptamine₃ and 5-hydroxytryptamine₄ receptor dual antagonist, on colonic
- 31 function in vivo. *J Pharmacol Exp Ther*. 1993 Jul;266(1):74-80.
- 32 104. Kishibayashi N, Miwa Y, Hayashi H, Ishii A, Ichikawa S, Nonaka H, et al. 5-HT₃
- 33 receptor antagonists. 3. Quinoline derivatives which may be effective in the therapy of
- 34 irritable bowel syndrome. *J Med Chem*. 1993 Oct 29;36(22):3286-92.
- 35 105. Siriwardena AK, Budhoo MR, Smith EP, Kellum JM. A 5-HT₃ receptor agonist
- 36 induces neurally mediated chloride transport in rat distal colon. *J Surg Res*. 1993
- 37 Jul;55(1):55-9.
- 38 106. Bjornsson ES, Chey WD, Ladabaum U, Woods ML, Hooper FG, Owyang C, et al.
- 39 Differential 5-HT₃ mediation of human gastrocolonic response and colonic peristaltic reflex.
- 40 *Am J Physiol*. 1998 Sep;275(3 Pt 1):G498-505.
- 41 107. Coates MD, Mahoney CR, Linden DR, Sampson JE, Chen J, Blaszyk H, et al.
- 42 Molecular defects in mucosal serotonin content and decreased serotonin reuptake transporter
- 43 in ulcerative colitis and irritable bowel syndrome. *Gastroenterology*. 2004 Jun;126(7):1657-
- 44 64.
- 45 108. Miwa J, Echizen H, Matsueda K, Umeda N. Patients with constipation-predominant
- 46 irritable bowel syndrome (IBS) may have elevated serotonin concentrations in colonic
- 47 mucosa as compared with diarrhea-predominant patients and subjects with normal bowel
- 48 habits. *Digestion*. 2001;63(3):188-94.
- 49 109. Tack J, Fried M, Houghton LA, Spicak J, Fisher G. Systematic review: the efficacy of
- 50 treatments for irritable bowel syndrome--a European perspective. *Aliment Pharmacol Ther*.
- 51 2006 Jul 15;24(2):183-205.
- 52 110. Banerjee S, Akbar N, Moorhead J, Rennie JA, Leather AJ, Cooper D, et al. Increased
- 53 presence of serotonin-producing cells in colons with diverticular disease may indicate
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 involvement in the pathophysiology of the condition. *Int J Colorectal Dis.* 2007
4 Jun;22(6):643-9.
- 5
6 111. Costedio MM, Coates MD, Danielson AB, Buttolph TR, 3rd, Blaszyk HJ, Mawe GM,
7 et al. Serotonin Signaling in Diverticular Disease. *J Gastrointest Surg.* 2008 May 20.
- 8
9 112. Porter AJ, Wattchow DA, Brookes SJ, Costa M. Cholinergic and nitrergic
10 interneurons in the myenteric plexus of the human colon. *Gut.* 2002 Jul;51(1):70-5.
- 11
12 113. Burleigh DE. Ng-nitro-L-arginine reduces nonadrenergic, noncholinergic relaxations
13 of human gut. *Gastroenterology.* 1992 Feb;102(2):679-83.
- 14
15 114. Tomita R, Tanjoh K, Fujisaki S, Fukuzawa M. Physiological studies on nitric oxide in
16 the right sided colon of patients with diverticular disease. *Hepatogastroenterology.* 1999 Sep-
17 Oct;46(29):2839-44.
- 18
19 115. Tam FS HK. The role of nitric oxide in mediating nonadrenergic non-cholinergic
20 relaxation in longitudinal muscle of human taenia coli. *Life Sci.* 1992;51:1277-84.
- 21
22 116. Hebeiss K, Kilbinger H. Differential effects of nitric oxide donors on basal and
23 electrically evoked release of acetylcholine from guinea-pig myenteric neurones. *Br J*
24 *Pharmacol.* 1996 Aug;118(8):2073-8.
- 25
26 117. Furness JB. Types of neurons in the enteric nervous system. *J Auton Nerv Syst.* 2000
27 Jul 3;81(1-3):87-96.
- 28
29 118. Fida R, Lyster DJ, Bywater RA, Taylor GS. Colonic migrating motor complexes
30 (CMMCs) in the isolated mouse colon. *Neurogastroenterol Motil.* 1997 Jun;9(2):99-107.
- 31
32 119. Tomita R, Fujisaki S, Tanjoh K, Fukuzawa M. Role of nitric oxide in the left-sided
33 colon of patients with diverticular disease. *Hepatogastroenterology.* 2000 May-
34 Jun;47(33):692-6.
- 35
36 120. Golder M, Burleigh DE, Ghali L, Feakins RM, Lunniss PJ, Williams NS, et al.
37 Longitudinal muscle shows abnormal relaxation responses to nitric oxide and contains altered
38 levels of NOS1 and elastin in uncomplicated diverticular disease. *Colorectal Dis.* 2007
39 Mar;9(3):218-28.
- 40
41 121. Furness JB, Costa M, Rokaeus A, McDonald TJ, Brooks B. Galanin-immunoreactive
42 neurons in the guinea-pig small intestine: their projections and relationships to other enteric
43 neurons. *Cell Tissue Res.* 1987 Dec;250(3):607-15.
- 44
45 122. Furness JB, Costa M. Neurons with 5-hydroxytryptamine-like immunoreactivity in
46 the enteric nervous system: their projections in the guinea-pig small intestine. *Neuroscience.*
47 1982 Feb;7(2):341-9.
- 48
49 123. Couture R, Mizrahi J, Regoli D, Devroede G. Peptides and the human colon: an in
50 vitro pharmacological study. *Can J Physiol Pharmacol.* 1981 Sep;59(9):957-64.
- 51
52 124. Grider JR, Cable MB, Bitar KN, Said SI, Makhlof GM. Vasoactive intestinal
53 peptide. Relaxant neurotransmitter in tenia coli of the guinea pig. *Gastroenterology.* 1985
54 Jul;89(1):36-42.
- 55
56 125. Grider JR, Cable MB, Said SI, Makhlof GM. Vasoactive intestinal peptide as a
57 neural mediator of gastric relaxation. *Am J Physiol.* 1985 Jan;248(1 Pt 1):G73-8.
- 58
59 126. Koch TR, Carney JA, Go L, Go VL. Idiopathic chronic constipation is associated with
60 decreased colonic vasoactive intestinal peptide. *Gastroenterology.* 1988 Feb;94(2):300-10.
127. Milner P, Crowe R, Kamm MA, Lennard-Jones JE, Burnstock G. Vasoactive
intestinal polypeptide levels in sigmoid colon in idiopathic constipation and diverticular
disease. *Gastroenterology.* 1990 Sep;99(3):666-75.
128. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med.* 1996 Apr
25;334(17):1106-15.
129. Sugihara K, Muto T, Morioka Y. Motility study in right sided diverticular disease of
the colon. *Gut.* 1983 Dec;24(12):1130-4.