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

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10 **Motility and Neurotransmitters**
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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.

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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).

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6 In a retrospective colonoscopy study in urban London, DD had a lower frequency in migrant
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8 Indians compared with other ethnic groups. These patients were significantly younger than
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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).
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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
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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
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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
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40 the other studies cited.
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50 2. *Structural pathogenetic factors*

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55 It has been suggested that a primary abnormality of muscularis propria in DD leading to its
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57 shortening and thickening, causing it to behave like myostatic contracture might exist and
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59 was the most consistent feature of diverticular disease (18). Muscle cells retain a normal,
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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
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8 pressure according to Laplace's law. The resulting hypersegmentation is thought to be
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10 important in the pathogenesis of the diverticula (20).
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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
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25 tensile strength (22, 23).
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32 Increased cross-linking of colonic collagen with age and in patients with diverticulosis may
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34 lead to rigidity and loss of tensile strength (22, 23), an increased synthesis of type III collagen
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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
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40 which may also contribute to the weakness (21).
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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
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50 normal controls (25).
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55 3. Age 56 57 58 59 60

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

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

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

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

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3 year age group (44). Younger patients are more commonly offered elective surgery which
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5 may explain this increase (45) (46).
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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.
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27 These traditional aetiological factors are summarised in Table 1.
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32 **Motility factors in pathogenesis**

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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).
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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).
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55 *1. Pressures*

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3 Left-sided diverticula which are pulsion pseudo-diverticula, occur most often in the sigmoid
4 colon, which has the smallest diameter, lowest compliance and therefore the highest
5 intraluminal pressures (56, 57).
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12 Not only do patients with diverticular disease have higher colonic intraluminal pressures than
13 control subjects (58) (25, 50, 59, 60) but it has also been shown that basal and post prandial
14 intraluminal pressures are higher in patients with symptomatic DD compared to those with
15 asymptomatic DD (61). The motility patterns in DD show similarity to those of Irritable
16 Bowel Syndrome (IBS) to the extent that some researchers have suggested that the two
17 conditions may be two forms of the same.
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29 Painter et al, 1965 used manometry and simultaneous cinematography to claim that
30 hypersegmentation led to formation of diverticula and this phenomenon was confirmed by
31 more recent studies (14, 62-64)
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39 Colonic transit studies in DD show conflicting results. Diverticular disease patients showed
40 delayed colonic transit which was expedited by bran (65). Conversely, another study showed
41 faster transit time between caecum and sigmoid colon in patients with DD compared to
42 controls but the mean total time of gastrointestinal emptying was no different in either group
43 (66). Similarly, Eastwood et al in 1978 found that 60 patients with DD failed to show
44 prolonged intestinal transit time, a reduced stool weight or increased intracolonic pressure
45 compared to the normal patients (67).
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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).

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3 Other studies have looked at the role of colonic pacemakers. The colon is thought to have at
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5 least four pacemakers, located at the caecal pole, the caeco-colonic junction, the mid
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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
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17 complained of constipation with pellet-like stools. These "dysrhythmias" may result from a
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19 disordered colonic pacemaker. The resulting colonic spasm seems to result in an intraluminal
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21 colonic pressure rise.
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29 3. *Heterogeneity in studies*

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34 There is conflicting evidence on the role of raised intramural pressure and increased
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36 myoelectrical activity in DD. The inconsistencies that arise are probably a result of a number
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38 of factors including methodological differences, heterogeneity of patients and disease states
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40 compounded by studies with relatively small numbers and differences in anatomical sites of
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42 investigation.
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48 On these grounds it is difficult to draw a firm conclusion from these investigations although it
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50 seems reasonable to accept that higher pressures and increased electrical activity are likely to
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52 be seen in patients with DD but it is unclear whether this a cause or result of the disease.
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55 A Summary of the motility factors implicated in the pathogenesis of DD is presented in Table

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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

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3 antidepressants. The tricyclic antidepressants display the same order of potency in inhibiting
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5 enteric and central reuptake of 5-HT.
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10 When colonic intraluminal pressure increases, enterochromaffin (EC) cells release 5-HT,
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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).
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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)
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29 5-HT evokes contractions of gut smooth muscle cells, either by stimulating 5-HT₃ receptors
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31 on nerve cells or 5-HT₂ receptors on muscle (81). Serotonin is also a potent intestinal
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33 secretagogue as administration of subcutaneous serotonin caused ileal secretion and reduced
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35 jejunal absorption of water and electrolyte (94), and serotonin also increased serosal to
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37 mucosal fluxes of chloride in animal models (95).
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43 Neuronal 5-HT₃ receptors are responsible for rapid depolarization responses in myenteric
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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
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49 involved in the peristaltic reflex (97-100) A. 5-HT₃ receptors are not just restricted to
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51 excitatory cholinergic motor nerves; 5-HT₃ receptor activation also releases "inhibitory"
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53 neurotransmitters in various regions of the gut, leading to smooth muscle relaxation during
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55 appropriate conditions (101).
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3 At present, the serotonin receptors with the greatest potential for therapeutic manipulation are
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5 the 5-HT₃ and 5-HT₄ receptor subtypes.
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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).
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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).
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34 *b. Serotonin and its role in GI pathology*

35 Serotonin in IBS has been extensively studied and most information is available in this area.
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37 Biopsies of patients with IBS had significantly lower mucosal concentrations of serotonin
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39 than normal controls along with lower concentrations of tryptophan hydroxylase which is a
40
41 rate limiting enzyme in serotonin synthesis (107). In another study, lower serotonin levels
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43 were observed in mucosal biopsy samples and post prandial blood samples from patients with
44
45 IBS with constipation (IBS-C) than in patients with IBS with diarrhoea (IBS-D) or in healthy
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47 volunteers (108) (82) with a lower level of SERT mRNA and SERT protein expression in the
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49 intestinal epithelial cells of IBS patients compared with that of healthy volunteers (107).
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57 Systemic review of IBS treatment concluded that there is strong evidence for the
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59 improvement of global IBS symptoms with two serotonergic agents: the 5-HT₄ selective
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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 HT₃antagonist/5-HT₄ agonist renzapride before their utility in IBS can be appraised (109)
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7
8 however as IBS is not the focus of this review, this will not be discussed further.
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12
13 Serotonin has been found to be increased in the colonic mucosa of resected specimens in
14 patients with DD (110). This relates to the increased colonic motility seen in DD. Therefore
15 serotonin antagonists may have a role in slowing progression of this disease and also
16 reducing symptoms, particularly in those patients whose predominant symptom is diarrhoea.
17
18 More directed therapy could also be instituted by carrying out biopsies in patients with DD
19 and identifying if there is an increase in serotonin and correlation with symptoms. However a
20 more recent study contradicts this finding where no difference has been found between
21 serotonin content in normal and Diverticular colonic mucosa (111)
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34 Serotonin which has been found to be an excitatory colonic neurotransmitter has been found
35 in early studies to be increased in colonic enterochromaffin cells (Banerjee, 2005). Serotonin
36 agonists may therefore may have a role in alleviating the symptoms and possible worsening
37 of DD. GABA which is thought to be an inhibitory agent, although not yet clearly identified
38 to have a role in DD, may have a converse role to serotonin.
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48 2. *Acetylcholine*

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53 Acetylcholine is an important neurotransmitter in normal bowel smooth muscle (112) that
54 mediates contraction via postsynaptic muscarinic M₃ receptors (113).
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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).
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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).
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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.
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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

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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
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8 pressure generated may lead to the formation of diverticula (120)
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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
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21 within the myenteric plexus (121). It is known that VIP has an inhibitory role in peristalsis
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23 (122-125).
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28 An abnormally low concentration of VIP in all the colon wall except mucosa, circular muscle
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30 and taenia has been shown in idiopathic constipation and would possibly correlate to excess
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32 segmenting and reduced propulsion (126, 127). Conversely, in diverticular disease, the VIP
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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
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45 disorders (127).
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51 Substance P is the main neurotransmitter after Acetylcholine for excitatory motor neurones.
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53 Other than the above study however, little is known about its role in Diverticular Disease
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55 (128). Similar to Ach however, it may be shown to be have attenuated activity in this
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58 condition.
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3 A summary of these neurotransmitters and their actions in the pathogenesis of DD is
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5 presented in Table 3.
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10 11 **The interplay between pathogenesis and neurotransmitters** 12

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14 As mentioned in the pathogenesis section, motility of colon in DD is abnormal. The effects
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16 seen as reported in the literature vary however it can generally be surmised that intraluminal
17
18 pressures are likely to be increased both basally and post prandially, (14, 25, 50, 58, 60, 64).
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20 This was also seen in right sided DD (129).
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26 Serotonin which has been found to be an excitatory colonic neurotransmitter has been found
27
28 in early studies to be increased in colonic enterochromaffin cells (110). Serotonin agonists
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30 may therefore may have a role in alleviating the symptoms and possible worsening of DD.
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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
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41 cause of pulsion diverticula. Similarly, a decrease of Nitric Oxide which is inhibitory is
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43 found.
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50 Conversely, Vasoactive intestinal polypeptide which is inhibitory is found to be increased
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52 and may related to formation of pulsion diverticula due to slow transit and constipation
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54 however there is no clear evidence of this at present.
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57 The interactions between these neurotransmitters and their subsequent effect on colonic
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59 motility and pathogenesis in DD is presented in Figure 1.
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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 myochosis
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

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	<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.
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For Peer Review

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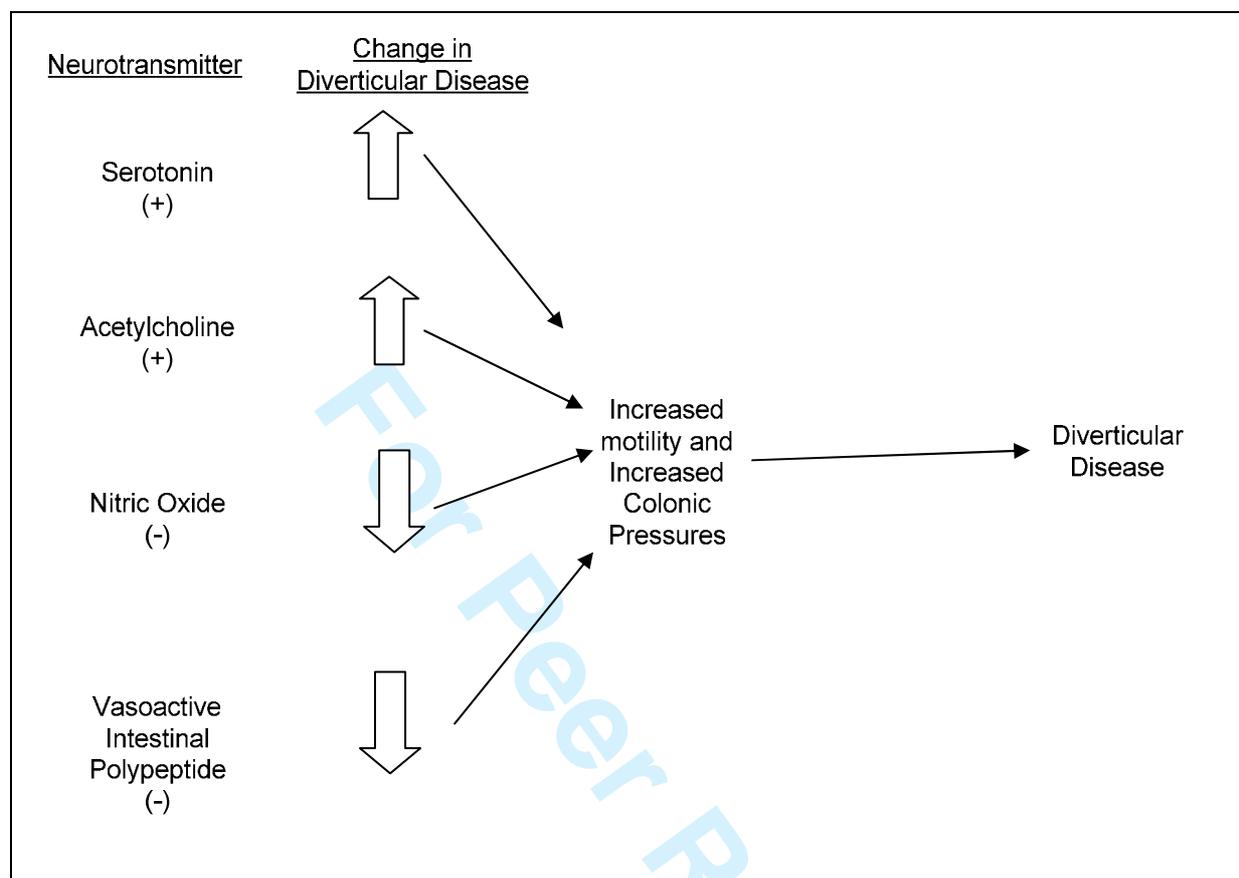
Table 3: Summary of characteristics and actions of neurotransmitters on the colon and the implications in Diverticular Disease

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

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Figure 1: Interactions between colonic neurotransmitters and implications on the Pathogenesis of DD



(+) excitatory

(-) inhibitory

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