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Neurotransmitters: The critical modulators regulating gut-brain axis†

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Abstract

Neurotransmitters including catecholamines and serotonin play a crucial role in maintaining homeostasis in the human body. Studies on these neurotransmitters mainly revolved around their role in the "fight or flight" response, transmitting signals across a chemical synapse and modulating blood flow throughout the body. However, recent research has demonstrated that neurotransmitters can play a significant role in the gastrointestinal (GI) physiology. Norepinephrine (NE), epinephrine (E), dopamine (DA), and serotonin have recently been a topic of interest because of their roles in the gut physiology and their potential roles in gastrointestinal and central nervous system pathophysiology. These neurotransmitters are able to regulate and control not only blood flow, but also affect gut motility, nutrient absorption, gastrointestinal innate immune system, and the microbiome. Furthermore, in pathological states such as inflammatory bowel disease (IBD) and Parkinson's disease, the levels of these neurotransmitters are dysregulated, therefore causing a variety of gastrointestinal symptoms. Research in this field has shown that exogenous manipulation of catecholamine serum concentrations can help in decreasing symptomology and/or disease progression. In this review article, we discuss the current state-of-the-art research and literature regarding the role of neurotransmitters in regulation of normal gastrointestinal physiology, their impact on several disease processes, and novel work focused on the use of exogenous hormones and/or psychotropic medications to improve disease symptomology.

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Conflict of Interest

The authors declare no conflicts of interest.

INTRODUCTION

It has recently become evident that the gut microbiota has the ability to influence physiological aspects of the body, including a direct communication to the brain from the gut (O'Mahony et al., 2015). In that regard, the gut microbiota has demonstrated unique functions associated with behavior, mood, and cognition that are currently being explored. The gut microbiota can interact with the chemical messengers involved in the transmission of information including monoamines such as 5-hydroxytryptamine (5-HT), also known as serotonin. Monoamines are not only synthesized in neural cells, but are also produced within the gastrointestinal system. Traditionally, it was thought that these monoamines functioned only in the central nervous system (CNS) as neurotransmitters and neuromodulators. However, it is now believed that monoamines influence a wide range of effects throughout the body. Several studies have suggested their fundamental roles in the gut microbiome and their indirect function in regulating the brain and cognitive processes.

The enteric nervous system (ENS), also known as the intrinsic nervous system, governs the function of the GI system. It can be found from the beginning of the esophagus to the anus embedded in the lining of the GI system. Therefore, although being in direct contact with the central nervous system (CNS) through innervation by the autonomic nervous system (i.e. sympathetic and parasympathetic), the GI tract has its own independent reflex activity. The interaction between the ENS and CNS, often described as the gut-brain axis, has been sparking researchers' interest for many years.

The gastrointestinal tract's impact on brain function has been recognized since the 19th century and in recent history, research on the gut-brain axis has largely been focused on digestive function. A plethora of studies now are exploring other possible physiological roles of the gut-brain axis and how dysfunction of this axis can cause various human diseases (Table 1). High co-morbidities exist between certain psychiatric symptoms and gastrointestinal disorders, a well-known example being anxiety and irritable bowel syndrome (IBS) (Reber, 2012). These connections indicate the relevance of the gut-brain axis in pathophysiology and therefore, modulators within the axis are appealing targets for novel therapeutic developments (Table 2). Neurotransmitters including serotonin, norepinephrine, epinephrine, and dopamine can play an important role in regulating gut-brain axis. Additionally, recent studies have suggested that the gut microbiota is a contributor to the pathophysiological effects of the gut-brain axis (Rhee et al., 2009).

This review article aims at discussing our most recent understanding of the interactions between neurotransmitters composed of catecholamines and serotonin, and the gut-brain axis. Here we highlight their synthesis, receptors, and relevant modulation of the human microbiota.

SEROTONIN

The brain-gut axis describes a network that communicates bi-directionally between the two organs where serotonin is a critical signaling regulator that modulates complex physiological functions, including gastric secretion or body temperature control (O'Mahony et al., 2015).

Consequently, a serotonin dysfunction in the gastrointestinal system could result in impairments in brain function, such as those involved in mood, sleep, and behavior (Delgado et al., 1990; Berger et al., 2009).

Synthesis

Tryptophan is a precursor in the biosynthesis of serotonin (Figure 1). Tryptophan is an essential amino acid, found in dietary proteins, including meats, dairy, and fruits (Friedman et al., 2012). Once it has been processed, tryptophan is able to cross the blood-brain barrier and metabolize into serotonin in the raphe nuclei within the brain stem (Le Floc'h et al., 2010). However, it is now known that much of serotonin synthesis occurs in the enterochromaffin cells (EC) and enteric nerves found within the gastrointestinal tract, where the transient receptor potential (TRP) cation channel TRPA1 activity critically control serotonin release (Mawe and Hoffman, 2013; Nozawa et al., 2009). The synthesis of serotonin is identical in the CNS and in the gut, where tryptophan is first converted to 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of enzyme. Then, aromatic amino acid decarboxylase (AAAD) almost immediately converts 5-HTP to 5-HT (Berger et al., 2009). Additionally, tryptophan could enter a separate, more dominant metabolic pathway, ultimately being converted to kynurenine via action by tryptophan-2, 3-dioxygenase (TDO) or the more readily available indoleamine-2,3-dioxygenase (IDO) (Schwarcz et al., 2012; Vécsei et al., 2013). The activities of these two enzymes are uniquely induced by different stimuli – for instance, TDO is prevalent in the presence of glucocorticoids and IDO is dominant during inflammatory events (Ruddick et al., 2006). One of the end products of kynurenine metabolism is kynurenic acid, an alpha 7 nicotinic acetylcholine receptor antagonist and N-methyl-d-aspartate (NMDA) receptor agonist at the glycine site, where kynurenic acid (KYNA) has been implicated to play a neuroprotective role (Vecsei et al., 2013). The other metabolite is quinolinic acid, an NMDA receptor and a known neurotoxin (Braidy et al., 2009). Due to the opposing roles of these two metabolites, their balance directly affects healthy and pathological states. Furthermore, it is important to note that when tryptophan is diverted to produce kynurenic acid and quinolic acid, the amino acid is then less available for serotonin synthesis. Only approximately 1% of available tryptophan goes on to metabolize into serotonin, and it has recently been demonstrated that 5-HT and kynurenine compete for available tryptophan, which leads to serotonin dysfunction during acute stress (Bender 1983; Keszthelyi et al., 2012). However, the complex role of kynurenine is beyond the scope of this review. There is a growing amount of evidence indicating that the gut microbiota regulates which metabolic pathway tryptophan will go, eventually affecting cognitive and local GI functions (O'Mahony et al., 2015).

Receptors

Serotonin binds to specific receptors within the GI tract to produce a diversity of responses. Serotonin receptors have been divided into seven classes (5-HT_1 to 5-HT_7) and consist of a total of 14 known serotonin receptors (Hoyer et al., 2002; Wirth et al., 2016; Palacios, 2016). 5-HT_1 has five receptor subclasses namely 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-$HT_{1F,}$ 5-HT_2 has three subclasses, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} whereas 5-HT_5 has two subclasses, 5-HT_{5A}, and 5-HT_{5B} (Hannon and Hoyer, 2008). Blockade of 5-HT_{1A} receptors

has been demonstrated to increase the severity of 2,4,6-Trinitrobenzene Sulfonic acid (TNBS)-induced colitis and exaggerated local and systemic neutrophil recruitment in a mouse model (Rapalli et al., 2016). On par with these findings, 5-HT_{1A} agonist delayed and mitigated the severity of colitis, counteracting the increase in colonic 5-HT content. In contrast, blockade of 5-HT_{2A} receptors improved global health conditions, reduced colonic morphological alterations, down-regulated neutrophil recruitment, inflammatory cytokines levels and colonic apoptosis. Antagonism of 5-HT_3, 5-HT_4, and 5-HT_7 receptor sites did not remarkably affect the progression and outcome of the pathology or only slightly improved it. 5-HT_4 agonists relieve visceral pain, as well as increase intestinal motility (Hoffman et al., 2012). The activation of 5-HT_4 has also been found to prevent apoptosis of enteric neurons and inflammation caused by axon terminal degeneration and autophagy (Liu et al., 2009). Additionally, following ingestion of irritants, EC cells release more serotonin, which binds to 5-HT_3 receptors in the GI to increase peristalsis and cause diarrhea as well as to 5-HT_3 receptors in the chemoreceptor trigger zone within the brain stem to stimulate vomiting (Rang 2003). Furthermore, due to the presence of serotonin in both the brain and the gut, selective serotonin reuptake inhibitors (SSRIs) are not only able to treat depression and other neurological disorders/syndromes, but are also capable of decreasing pain and other symptoms associated with chronic GI disorders (Vanuytsel et al., 2014); these results were obtained independently to the gut-brain axis.

Serotonin in the GI tract: interaction with the microbiota

The gut microbiome refers to the population of microorganisms residing in the gut. Recently there has been increased interest in understanding how the gut microbiota influences the brain-gut axis. It has been demonstrated that patients suffering from IBS had significantly lower mucosal and higher systemic concentrations of both 5-HT and KYNA in comparison to healthy controls (Keszthelyi et al., 2013). This study disproved the hypothesis that increasing activation of the kynurenic pathway results in serotonin dysfunction; rather, it was suggested that both substances were released into the systemic compartment leading to complications in the gut. Interestingly, this study also uncovered a correlation between mucosal concentrations of KYNA and 5-HT in IBS patients and psychological state changes, evaluated using the Hospital Anxiety and Depression Scale and the Symptom Checklist-90. This indicates a possible secondary consequence due to changes in the stability and diversity of the microbiota found in IBS (Keszthelyi et al., 2013).

Serotonin synthesis not only has to compete for its precursor tryptophan from undergoing the kynurenic pathway, but the gut microbiota itself could directly utilize tryptophan, reducing its availability to the host. Bacterial species, such as *Escherichia coli, Achromobacter liquefaciens*, and *Paracolobacturm coliforme*, break down tryptophan into indole via the enzyme tryptophanase. By-products of this conversion include pyruvate, which can be utilized in other metabolic functions, such as in cellular respiration, and ammonia, which in large amounts is toxic to the intestinal epithelium (Smith and Macfarlane, 1997).

A balanced gut microbiota is necessary for the physiological function of the mucosa's immune defense. Several studies have indicated that presence of bacteria is necessary to

trigger normal immune responses. For instance, compromised expression of certain toll-like receptors (TLRs), responsible for differentiating pathogenic bacteria from harmless commensal ones and decreased IgA secretion were found in germ-free, gut microbiota-deficient, animals (Wostmann et al., 1970; Shanahan, 2002; Grenham et al., 2011). When the mucosa was allowed to colonize in germ-free animals, however, the mucosal immune system function is salvaged (Umesaki et al., 1995). Serotonin contributes to the immune response as 5-HT receptors have been found on lymphocytes, monocytes, macrophages, and dendritic cells (Cloez-Tayarani and Changeux, 2007). Factors that negatively affect serotonin's immune-modulatory role could result in intestinal inflammation and the pathogenesis of gastrointestinal disorders, including Crohn's disease, ulcerative colitis, celiac disease and diverticulitis (Shaw et al., 2010). In animal models, inducing inflammation with an infection resulted in a downregulation in sodium-dependent serotonin transporter, SERT, while the 5-HT and EC cell number increases (O'Hara et al., 2006; Wheatcroft et al., 2005). The precursor for serotonin (5-HTP) also promotes actin remodeling seen in microvilli development for phagocytic activity in immune cells and induces extracellular signal-regulated kinases (ERK) phosphorylation in macrophages (Nakamura et al., 2008).

Recent studies from our laboratory showed that increased levels of serotonin can enhance quorum sensing in *Pseudomonas aeruginosa* both *in vitro* and *in vivo* (Knecht et al., 2016). Quorum sensing is the process by which bacteria in close proximity are able to communicate with one another through chemical signaling (Castillo-Juárez et al., 2015). This bacterial communication is necessary for biofilm formation, swarming motility, induction of gene expression, exopolysaccharide production, and the exchange of virulence factors (Sauer, 2002; Liu et al., 2015; Abraham, 2016). Therefore, high serotonin levels resulted in increased *P. aeruginosa* pathogenicity by enhancing biofilm formation and elaboration of virulence factors, *in vitro* (Knecht et al., 2016). In a mouse model, we observed that animals treated with exogenous serotonin and infected with *P. aeruginosa* exhibited an increase in intestinal bacterial load and mortality compared to untreated animals. The administration of exogenous serotonin enhanced the production of pro-inflammatory cytokines, increased biofilm formation on mouse intestines and worsened intestinal pathological manifestations. Intriguingly, serotonin was able to restore the ability of avirulent quorum-sensing *P. aeruginosa* mutant to cause intestinal infection in mice. These discoveries call for further research in patients with high levels of serotonin whether due to physiological, pharmacological, or pathological reasons. Drugs such as SSRI's used for the treatment of different mental disorders with the goal of increasing serotonin, despite being useful in the management of psychiatric issues, may also present negative side effects on patients. The action exerted by serotonin can be various and is dependent on the subtype of receptor with which the interaction occurs. Altogether, results suggest that serotonin plays both beneficial and detrimental roles, particularly in the gut. Therefore, therapeutic strategies targeting serotogenic system should be carefully designed considering the antithetical effects of these monoamines.

CATECHOLAMINES

Catecholamines are monoamines comprised of a catechol group and an amine side chain. The synthesis and degradation of these amines are well defined in the literature and have a

wide impact on the human body. There are three main catecholamines: norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine; norepinephrine and epinephrine are also known as the “fight or flight” peripheral catecholamines while dopamine is a central acting catecholamine. It involves numerous neural pathways such as reward pathway via the nucleus accumbens. Dopamine is commonly associated with the ‘pleasure system’ of the brain, providing feelings of enjoyment and exhilaration.

Synthesis

Norepinephrine and epinephrine are mainly produced in two places; first being at the end of postganglionic sympathetic nerve fibers (local response), and second being synthesized by chromaffin cells of the adrenal medulla (systemic response). The local response is mainly controlled by the hypothalamus-pituitary adrenal axis while the systemic response is neural mediated. Dopamine, on the other hand, is synthesized mainly in the brain.

All catecholamines are derived from L-tyrosine. Using this base molecule, tyrosine hydroxylase, with co-factors, tetrahydrobiopterin and oxygen, convert L-tyrosine to L-dopa (Figure 3). Tyrosine hydroxylase is the rate limiting enzyme in the overall synthesis of catecholamines (Shiman et al., 1971). L-dopa is further manipulated into Dopamine with the enzyme DOPA decarboxylase and cofactors pyridoxal phosphate. Dopamine is the first catecholamine made and is found in the central nervous system. In peripheral tissues, dopamine is further manipulated by dopamine B-hydroxylase, with cofactors ascorbate and oxygen, to form norepinephrine and subsequently by phenylethanolamine N-methyltransferase, with cofactor S-adenosylmethionine, to finally make epinephrine. The last three products (dopamine, norepinephrine, and epinephrine) in this biosynthetic pathway are classified as catecholamines and each have specific properties and functions on various organ systems.

The most important enzyme in catecholamine synthesis pathway is tyrosine hydroxylase. Extensive research has been conducted to determine regulation of this enzyme, which ultimately regulates the production of all three catecholamines. The main mechanism is through endogenous neuropeptide Y (NPY). The mechanism through which this works is complex, but mainly works by inhibiting Ca^{2+} influx through L-type Ca^{2+} channels through PKC pathway which subsequently inhibits neuronal depolarization and halts catecholamine synthesis (McCullough and Westfall, 1996). Other tyrosine hydroxylase inhibitors, such as alpha-methyl-p-tyrosine, has been shown to decrease overall synthesis of catecholamines (Thompson et al., 1983).

Receptors

A number of studies have been carried out to determine the receptor of choice for norepinephrine and epinephrine. Their affinities do not change in the gut. Epinephrine mainly exerts its effects on α_1 and β_2 while norepinephrine exerts its effect on α_1 and α_2 with minimal, if any, effect on β_2. This subtle difference determines each catecholamine’s specific effect on the entire gut, in terms of absorption, blood flow and motility. Dopamine on the other hand, despite being the precursor to epinephrine and norepinephrine, has its own receptors (D_1 to D_5). As of late, dopamine has been accepted as another major

catecholamine that is involved with gut homeostasis. In terms of receptor location, D_4 receptors are found only in the mucosal layer, whereas D_1, D_3, and D_5 receptors can be found in both the nerve ending layer of the intestinal wall as well as the gut mucosa, and lastly D_2 receptors are found only in the nerve ending layer of the intestinal wall. Studies have pointed towards the fact that the D_2 receptor is the major mediator of the endogenous effects of dopamine (Sclafani, 2001).

Catecholamines in the GI tract: blood flow

The major blood supply to the splanchnic region comes from the celiac trunk, superior mesenteric artery, and inferior mesenteric artery and all three sources eventually flow into the portal system aimed into the liver. Hemodynamics with the administration of catecholamines is a complex subject and many variables come into play such as blood volume, organ failure, and concurrent hormones. Broadly, norepinephrine mainly acts on the alpha receptors at all concentration ranges which results in vasoconstriction, increasing vascular resistance, and a decrease in overall blood flow to the intestines. Norepinephrine is a last resort drug for patients with hemodynamic instability for which stability cannot be reached with the other catecholamines. Compared to its counterpart, epinephrine stimulates beta receptors leading to vasodilation at low doses, which would increase blood flow, and vasoconstriction at high doses similar to norepinephrine. These effects are seen in patients with a normal cardiac output and changes in heart function or during times of stress often skew these effects. Many studies have been performed on septic patients, patients with renal failure as well as heart failure and conflicting results have been found (Thompson et al., 1983; Abrass et al., 1985; Richardson and Withrington, 1982).

Although dopamine has five receptors, the main vasoactive receptor is the D_1 receptor, which stimulates adenylyl cyclase and increases protein kinase C activity. Dopamine receptors are primarily found in the mesenteric, coronary, cerebral, gastric, and hepatic vasculature. Dopamine is a unique catecholamine because its receptor affinity is concentration dependent. At low doses (i.e. 1–3 μg/kg), it preferentially binds to its D_1 receptors. At medium doses (i.e. 3–10 μg/kg) it additionally binds to β_1 adrenergic receptors. At high doses (> 10 μg/kg) it additionally binds to α_1 adrenergic receptor. Overall, low dose dopamine is known to cause vasodilation (similar to beta adrenergic receptors) which increases splanchnic blood flow through interaction with D_1 receptor. At high doses, it can be considered similar to other catecholamines and be classified as a vasoconstrictor and decrease splanchnic blood flow (Grayson and Oyebola, 1983).

Catecholamines in the GI tract: nutrient absorption

Epinephrine and norepinephrine play a major role in changing absorption rates as per the needs of human body. In a study comparing glucose concentrations between jejunum arterial flow versus venous flow before and after administration of intravenous epinephrine, a significant hyperglycemic response has been demonstrated post-injection compared to controls. To localize the specific receptor subtype, they co-administered either propranolol, a beta receptor antagonist, and/or prazosin, an alpha receptor antagonist, with the catecholamine. The researchers concluded that simulation of the beta receptor was the cause of the hyperglycemic response (Grayson and Oyebola, 1983). Furthermore, epinephrine co-

administered with thyroid hormone caused a significant overall increase in glucose concentrations compared to thyroid hormone alone in a dose dependent manner (Olaleye and Elegbe, 2005). This shows that epinephrine has the ability to potentiate the actions of other endogenous hormones.

Besides glucose absorption, epinephrine also affects absorption of several other molecules and ion transporters. Using rat jejunums, epinephrine showed increased rates of Dextran absorption (4000 Da) via paracellular route. Interestingly, absorption rates varied depending on the stimulation of specific receptor. Alpha and beta stimulation showed an increased rate of absorption compared to controls. Beta stimulation alone (co-administration with alpha antagonists) showed an increase rate of absorption but not to the extent seen in of alpha stimulation alone or with alpha and beta stimulation (Kamio et al., 2005). In addition, histological examination of jejunum mucosa showed no change.

A similar phenomenon occurs with the transport of oligopeptides in the gut. Epinephrine increases the concentration of oligopeptide transporters on the apical surface of mucosal intestinal cells to augment the uptake of oligopeptides from the lumen (Berlioz et al., 2000). Epinephrine has also been shown to increase transporter rates in transporters such as: Na^+/H^+ antiporter (Isom et al., 1987), $Na^+/K^+/2Cl^-$ cotransporter (Haas et al., 1995), Na^+/glucose cotransporter (Ishikawa et al., 1997), and benzyl-penicillin transporter via transcellular movement (Skowronski et al., 2000). Taken overall, the alpha receptor subtype is the predominant receptor that governs intestinal absorption rates. In terms of beta receptors, conflicting evidence has been shown in which concurrent beta receptor antagonism and alpha receptor stimulation result in a higher absorption rate than alpha and beta receptor stimulation.

Compared to the other catecholamines, dopamine plays a small role in regulating electrolyte absorption in the GI tract. First, studies using rabbit ileum showed that dopamine stimulation increased Na^+ and Cl^- influx with concurrent decrease in Ca^{2+} influx. The researchers in this study concluded that dopamine's cause of increased absorption acted indirectly through cross reaction with α_2 receptors which can happen at medium to high doses of dopamine (Donowitz, 1983). A conflicting study showed an opposite reaction with dopamine stimulation using rat jejunums who were fed a high salt diet. An inverse correlation was found with Na+/K+ ATPase activity and dopamine concentration; this relationship was abolished with the administration of dopamine synthesis antagonists (Vieira-Coelho et al., 1998). Lastly, dopamine synthesis blockers has been found to play a role in mucosal protection against ulcer formation. Administration of catechol-O-methyl transferase (COMT) inhibitors with and without concurrent administration of adrenergic receptor blockers, both alpha and beta blockers, showed a dose dependent increase in bicarbonate secretion in rat duodenum via stimulation of peripheral D_1 receptors (Flemstrom et al., 1993). Dopamine is likely to play a role in nutrient-derived post ingestive signaling and reward (Ren et al., 2010). It is already known that oral stimulation with glucose produces a significant increase in dopamine release; interestingly, a significant increase in glucose was also seen in ageusic animals (de Araujo et al., 2008). Furthermore, intragastric infusions of glucose stimulated significantly higher levels of dopamine levels in the nucleus accumbens compared to isocaloric intragastric infusions of L-serine (Ren et al., 2010). Taken together,

these studies provide evidence that dopamine efflux in the reward pathway is produced by direct stimulation of the gastrointestinal tract.

Catecholamines in the GI tract: interaction with the innate immune system

The gut hosts a wide variety of bacteria that are essential for human well-being. They help in digestion, produce vitamins, and protect against harmful bacteria. However, because of the constant interaction with bacteria, the gut must have a large immune system and innate properties to protect the host from invading organisms. The majority of catecholamines that interact with the enteric system is mediated through postganglionic sympathetic neurons located in the celiac, superior mesenteric, and inferior mesenteric ganglia. These neurons interact with the intestines at the serosal surface and innervate the vascular beds as well as the enteric nervous system. These post-ganglionic sympathetic axons project to almost every lymphoid tissue throughout the body. Specifically, within the gut the majority of these axons terminate in the Peyer's patches, intestinal aggregates of lymphoid follicles, while a few of these fibers terminate in the lamina propia (Janig, 2014). Interestingly, these axons do not make the traditional synaptic contacts as they would in the majority of the body (Vizi and Elenkov, 2002). Instead, the norepinephrine that is released from axon terminals must diffuse through a network of tunnels, sometimes travelling up to 1 μm, before interacting with postsynaptic receptors. Therefore, sympathetic innervation of the local sections of lymphoid tissue can be activated with relatively few sympathetic postganglionic axons (Dunn et al., 1999). In addition, serotonin and catecholamines released from the neurons can influence the microbiota present in the gut leading to altered release of cytokines and bacterial molecules (Figure 3).

The gut innate immune system provides the first line of defense against foreign pathogens. Macrophages constitute an integral part of gut innate immune system that circulate and provide constant surveillance of GI pathogens. Recent research has shown that depending on the location of the macrophages, they express a high degree of gene-expression specialization. Mucosal macrophages (Farache et al., 2013) are located in close proximity to the intestinal lumen while their counterparts, muscularis macrophages (Bogunovic et al., 2009) are located in the region between the two gut muscle layers alongside enteric neurons. It is found that these two distinct group of macrophages play different roles in both protection and regulation of gut mucosa and motility. The mucosal macrophages are involved in constant surveillance for pathogenic bacteria and play a role in tolerance to dietary antigens (Cervi et al., 2014). On the other hand, the muscularis macrophages regulate the enteric neurons and peristalsis. Furthermore, it is found that subpopulations of B-cells, neutrophils, and macrophages, specifically muscularis macrophages, express a large number of β_2 adrenergic receptors (Cervi et al., 2014). It is also well described in the literature that alpha adrenergic signaling boosts inflammation while beta adrenergic signaling suppresses both innate and adaptive immunity (del Rey and Besedovsky, 2008; Guereschi et al., 2013). Taken together, it is postulated norepinephrine can mitigate the local pro-inflammatory state induced by mucosal macrophages via the muscularis macrophages. In addition, due to the close proximity of muscularis macrophages to enteric neurons, the local concentration of norepinephrine can lead to local suppression of inflammation and not have systemic effects (Farache et al., 2013; Abrass et al., 1985). This immune suppression occurs by

downregulation of the Th1 immune response as evident by a decrease in INF-γ, TNF-α and IL-2 production (Kin and Sanders, 2006).

In terms of immunoglobulins, secretory IgA are constantly secreted transluminally across epithelial cells to provide protection along the mucosa. Adrenergic receptors in proximity to the IgA secretory B-cells and immunoglobulin receptors can be stimulated to release IgA and increase the concentration of IgA receptors, via mRNA expression (Mestecky and Russell, 2009), in both porcine large and small intestines (Macpherson and Slack, 2007). Rats in which were chronically stressed showed increased IgA positively stained intestinal cells. When these rats underwent sympathectomy with 6-hydroxydopamine, the number of IgA immunoreactive cells were significantly decreased (Reyna-Garfias et al., 2010). Further evidence of stress hormones affecting IgA secretion were shown in marathon runners where biopsies of their intestines confirmed the increased concentration of IgA (Nilssen et al., 1998).

Interestingly, newer evidence is suggesting that catecholamines not only suppress the host immune system, but also augments and stimulates bacterial virulence factors and pathogenesis of bacterial disease. In a non-immune manner, stress hormones can also interact with the bacteria and the environment to aid bacteria to thrive rather than affecting the host immune system (Lyte, 2004). Gram-negative bacteria incubated in nutrient deficient environments to mimic the intestinal environment showed a several log-fold increase in growth compared to control group following exposure to catecholamines (Lyte and Ernst, 1992; Lyte et al., 1997). Many bacteria have shown this response including *Campylobacter jejuni* (Cogan et al., 2007), *Escherichia coli* (Lyte et al., 1996; Diard et al., 2009), *Helicobacter pylori* (Doherty et al., 2009; Lyte, 2010), *Pseudomonas aeruginosa* (Li et al., 2009; Hegde et al., 2009), and *Salmonella enterica spp* (Bailey et al., 1999). The mechanism of this action is not quite fully understood but it is postulated that the structural presence of hydroxyl groups at the 3 and 4 position rather than receptor stimulation at the bacterial level causes this effect (Bailey et al., 1999). Studies aimed at determining whether alpha and beta blockers co-administered with catecholamines affect bacterial growth, observed no significant variation therefore further supporting the fact that the structure of these catecholamines is the mechanism through which they exert their effects.

Survival of bacteria depends partly on their ability to sequester iron. Pathogenic bacteria secrete siderophores to combat the human sequestration of iron via lactoferrin/transferrin glycoproteins (Freestone et al., 2000). These siderophores have similar structural resemblance to catecholamines with the 3,4 dihydroxyl group (Bailey et al., 1999). Catecholamines were found to facilitate the removal of iron from human lactoferrin and transferrin in a dose and time dependent manner which also correlated with bacterial growth. The mechanism by which this happens occurs through the formation of direct complexes with Fe^{3+} and the subsequent reduction of Fe^{3+} to Fe^{2+} which therefore releases the iron to be available to bacteria (Freestone et al., 2000).

In addition to iron release, catecholamines are able to stimulate the expression of various virulence factors which further facilitate bacterial invasion. Norepinephrine has been shown to increase the expression of K99 pillus adhesions (Lyte et al., 1997), release of shiga-like

toxins (Lyte et al., 1996) of *E. coli* which then allowed more bacteria to adhere to the colonic wall. Norepinephrine also increase the expression of flagella and type III secretion systems in Salmonella (Moreira et al., 2010). Furthermore, iron can also increase the expression of flagella and type III secretions in Salmonella, norepinephrine therefore aids in Salmonella's growth via an indirect manner (Bearson et al., 2010; Ellermeier and Slauch, 2008).

Catecholamines in the GI tract: gut Motility

The gut is highly sensitized by the sympathetic system and motility is highly effected. Epinephrine's preference towards beta adrenergic receptors usually cause smooth muscle relaxation, therefore slowing the overall transit and decreasing the amount of migratory motor complexes. Interestingly, if a beta adrenergic receptor is blocked through phentolamine administration, the remaining alpha receptors can cause intestinal smooth muscle contraction, speeding up overall intestinal motility (Hirst and Silinsky, 1975). Studies using rat colon showed that administration of catechol-O-methyltransferase inhibitors, which inhibits degradation of catecholamines, inhibited longitudinal muscle contraction therefore decreasing the colonic transit. When co-administered with a β_2 adrenergic receptor blocker, the colonic inhibition was abolished suggesting that beta adrenergic stimulation in the colon participate in inhibition of colonic transit. Further supporting this evidence, acute and chronic stressed rats showed increased circulating norepinephrine causing increase gene transcription of Ca^{2+} L-type channels in colonic smooth muscle which resulted in enhanced colonic motor function (Tache et al., 2001; Choudhury et al., 2009).

The effects of D_2 receptors are specific and distinct. Comparing D_2 to D_3 knock-out mice, D_2 knock-out mice showed increased total GI tract and regional colonic motility. This shows that D_2 mediated effects slow GI overall transit time, similar to its catecholamine counterparts. In addition, the same study showed that D_2 knock mice had severe problems in weight gain. These mice with faster intestinal tract time had ate and drank more but failed to gain weight normally when compared to D_3 knockout mice and resulted in an increased dry weight and water content of the stools, suggesting possible absorption problems (Gagon, 1970; Costa and Furness, 1976). Furthermore, D_2 knockout mice had an enhanced peristaltic reflex therefore it follows that D_2 mediation inhibition occurs within the ganglia which affect the microcircuits that govern overall peristaltic and/or secretory function. This hypothesis is further supported by the aforementioned location of D_2 receptor found at the neuritic process myenteric and submucosal neurons (Li et al., 2006). This location is of importance because it is in close proximity of acetylcholine releasing neurons. Dopamine and D_2 agonist have been shown to reduce the release of acetylcholine from enteric neurons (Kusunoki et al., 1985).

It is also postulated that dopamine plays a role in gastric emptying. Gastric empting rates as well as dopamine efflux were measured comparing administration of high versus low caloric lipid emulsions. There was a direct correlation between the two, high caloric emulsion was related to high dopamine concentrations in the ventral and dorsal striatum as well as slower gastric emptying and vice versa. There are a lot of other factors that also come into play

including gastric distension (Feifel et al., 2003), caloric density, gastric secretion of ghrelin, physical factors, and CCK (Ferreira et al., 2012).

NEUROTRANSMITTERS AND DISEASES

Serotonin and catecholamines are extensively involved in numerous physiological processes and as such, changes in their levels and/or activity are associated with a myriad of human diseases (Table 1) (Berger et al., 2009; O'Mahony et al., 2015). Recently there has been a renowned interest in understanding the role of neurotransmitters in a number of brain disorders including autism as patients suffering from these disorders exhibit profound gut dysbiosis (De Angelis et al, 2015; Rosenfeld, 2015; Moos et al., 2016). Future investigations will help in deciphering the contribution of neurotransmitters in modulating gut-brain axis during autism.

Catecholamine levels affect the whole body, from the brain with sensation of happiness to the regulation of the GI tract. It is therefore not surprising that diseases of the CNS can have a profound impact on the ENS. Parkinson disease (PD) is a prime example of what happens when the intricate connections between CNS and ENS are jeopardized. It is a neurodegenerative condition that is mainly characterized by the loss of dopaminergic neurons in the nigrostriatal and mesolimbic pathways including the ventral tegmental area (Sugama and kakinuma, 2016). As first described by James Parkinson, GI dysfunction is an important feature of PD. It represents the most common autonomic disorder of the disease. In the ascending colon of PD patients the levels of DA were found to be decreased, and thus it seems to be a major candidate for the impairment of GI function. DA has been shown in rats to modulate fluid absorption, motility, blood flow, exocrine secretion, and cytoprotection (Natale et al., 2008). Dopaminergic degeneration of the substantia nigra pars compacta in rats induced by injection of 6-hydroxy-dopamine is associated with neurofunctional and neuroanatomical changes of the brain-gut axis circuitry controlling but not limited to the stomach. The delayed gastric emptying associated with these alterations is similar to the gastric dysfunctions observed in PD patients (Toti and Travagli, 2014). Further down the GI tract, clinical studies comparing colonic tissue from 11 patients with advanced Parkinson disease to control subjects showed that patient with Parkinson disease had substantially fewer dopaminergic myenteric neurons (Singaram et al., 1995). Nonetheless, as a way to alleviate most of the symptoms associated with the neurological condition the use of subthalamic deep brain stimulation may be recommended for PD patients. This revolutionary modality has been suggested to improve gastric motility and reduce GI dysfunction (Krygowska-Wajs et al., 2016) amongst other benefits such as tremor reduction. As for diagnostic purposes, recent work demonstrated that peripheral neurons contained in the ENS are affected by Lewy pathology which can appear before first symptoms. Therefore, a GI biopsy can be a source of biomarkers in PD (Corbillé et al., 2016), underlying the importance of early detection.

Yet another intestinal disorder dependent on hormone levels, IBS causes abdominal pain, bloating, diarrhea, and constipation. Its cause is not well understood but symptoms can be controlled by managing diet, lifestyle, and stress. Medications and counseling may be required. Patients with IBS show evidence for increased noradrenergic activity consistent

with downregulation of presynaptic inhibitory α_2 adrenergic receptors. Activity within the central arousal circuits is biased toward greater excitability and reduced inhibition in IBS. These abnormalities could be explained by an early life trauma as explained by Berman and al. (Berman et al., 2012). Evidence suggests a great deal of differences in neuroendocrine levels in women during sleep between those suffering from constipation-predominant IBS and those suffering from diarrhea-predominant IBS. Indeed, when compared to controls, the constipation-predominant group demonstrated significantly increased levels of E and NE whereas the diarrhea-predominant group demonstrated significantly lower NE. Such results suggest that neuroendocrine profiles during sleep may help us understand symptom expression in IBS (Burr et al., 2009). Since a large factor of IBS is due to stress, enhanced stress responsiveness has been implicated as a possible mechanism. However, although dysregulation in the stress-response systems such as the hypothalamic-pituitary-adrenal axis and mucosal immune function have been demonstrated in IBS, they seem not to have a primary role and the severity of the disease and abdominal pain (Chang et al., 2009).

When inflammation of the intestine resulting from an autoimmune reaction occurs it is often referred to as IBD. There are two major types of IBD, ulcerative colitis (UC) and Crohn's disease (CD). An interesting study looking at the two types, side by side, noted that NE tissue levels in both inflamed and non-inflamed colonic mucosa were markedly lower in CD, but not in UC. However, there were increased levels of L-dopa and decreased levels of DA in both diseases, resulting in a reduction in DA/L-DOPA tissue ratios indicating low L-amino acid decarboxylase activity (Magro et al., 2002). The treatment of UC with D-2 receptor agonists decreased its severity in animal models by attenuation of enhanced vascular permeability and prevention of excessive vascular leakage. The fact that dopamine agonists could rescue normal function is evidence that the impairment of the dopaminergic system is a feature of IBD pathogenesis (Tolstanova et al., 2015).

In the CNS, serotonin is a key player within cognitive spheres involved in mood and behavior, as found in pathological models (O'Mahony et al., 2015; Collins et al., 2012). Chronic stress in particular is well understood to cause adverse effects in behavior, cognition, as well as in gut microbiota. It has recently been shown that administration of probiotics can improve chronic stress-induced depression. Rats within the study were subjected to 21 days of restraint stress followed by behavioral testing and biochemical analysis, and every day, *Lactobacillus helveticus* NS8 was supplemented until the end of the experiment with SSRI citalopram serving as a positive control. The study determined that the addition of the daily probiotic improved anxiety, depression, and cognitive dysfunction comparable to the positive control. Plasma levels of hormones released from stress (corticosterone, adrenocorticotropic hormone, and norepinephrine) were also found to decrease (Liang et al., 2015). Another study determined that microbiota is necessary to initiate of behavioral despair and anxiety-like behavior, such that microbiota depletion resulted in decreased anxiety. Mice were treated with antibiotics from weaning onwards to assess potential changes in adulthood. Not only was decreased anxiety-like behavior was observed in the mice, but deficits in cognition were evident as well. In addition, neuromodulators, including tryptophan, monoamines, and neuropeptides, and brain-derived neurotrophic factor expression were greatly reduced when evaluated during adulthood.

These results indicate that early life events can influence adult behaviors via neurochemical changes that resulted from altering the microbiota (Desbonnet et al., 2015).

The diseases linked to a dysregulation in serotonin levels can affect virtually any organ of the gastrointestinal tract. Increasing serotonin availability between neurons and their effector cells is the primary mechanism by which re-establishment of normal physiological function can be achieved. The relationship between esophageal disease and serotonin is one that is primarily centered on the use of serotonin reuptake inhibitors (SRIs) and serotonin agonists for treatment. At this time, SRIs and serotonin agonists are only sparsely used in the management of upper GI tract disorders. Nevertheless, studies are looking into their use to treat esophageal motility disorders (Karamanolis et al., 2015; Scheerens et al., 2015), gastroesophageal reflux disorders (Ostovaneh et al., 2014), and hypersensitive esophagus (Dickman et al., 2014; Viazis et al., 2011; Viazis et al., 2012). Recent research analyzing the effectiveness of the serotonin agonist Buspirone in the treatment of esophageal dysfunction associated with systemic sclerosis demonstrated an increase in esophageal motility in 30 patients (Karamanolis et al., 2015). Other investigations inspired by this study tested greater levels of Buspirone, amongst other similar compounds, and found that serotonin agonists produce enough effect to warrant greater study and consideration (Scheerens et al., 2015). A study by Wu et al. presented evidence that serotonin disrupts tight junctions in the esophagus by reducing the expression of their proteins (Wu et al., 2016). This study calls for greater investigation since the breakdown of tight junctions could result over time in dramatic consequences such as tumor progression and metastasis.

The effect of serotonin on the stomach is a widely discussed topic but very few studies have found reliable data. Nonetheless, a series of studies have demonstrated that serotonin may be an aggravating factor in dyspepsia. In addition, it has been proposed that SRIs may exacerbate upper gastrointestinal bleeds in patients with *Helicobacter pylori* infections (Dall et al., 2011). Furthermore, evidence shows that a combination of SRIs and aspirin significantly improves the likelihood of gastrointestinal bleed (Wang et al., 2014).

Also, elevated levels of mucosal serotonin in the small intestine, such as seen in celiac disease, can cause increased immune response in the gut and thus have negative effects on patients (Di Sabatino et al., 2014). Unwanted symptoms from serotonin excess can also be found in ulcerative colitis and Crohn’s Disease (Guseva et al. 2014; Kidd et al. 2009; Minderhoud et al. 2007; Yu et al. 2016).

Interestingly, in patients suffering from irritable bowel disease, as previously seen with opposed levels of catecholamines, an increase in serotonin is correlated with diarrhea whereas a decrease is correlated with constipation (Yu et al., 2016; Zang et al., 2016). Irregularities in serotonin levels have also been observed in diverticulitis where a dysfunction in serotonin transporters results in inflammation compromising the intestinal wall (Costedio et al., 2008).

The effects of serotonin on the GI tract are numerous, its benefits in the treatment of pathologies still seem uncertain. The fact that serotonin application results in opposite outcomes in various disease processes is contradictory. Therefore, care providers should

proceed with caution when considering to prescribe medications that increase the stimulation of serotonin receptors.

ADENOSINE TRIPHOSPHATE

Adenosine triphosphate (ATP) is classically known as the major driving force for chemical reactions in the body, but ATP can also participate in the transduction of neurological signals by acting as a neurotransmitter or co-transmitter. As a neurotransmitter, ATP and adenosine act primarily on the purinergic receptors of class P1, P2X, and P2Y. P1 and P2Y are G-protein coupled receptors, while P2X is a ligand-gated ion channel. In the enteric nervous system, it is unclear what role purinergic receptors play, but it is known that the receptors can be found in the gut, particularly in the myenteric plexus. The data on these receptors has not yet provided a clear picture of the role these receptors play. On the one hand, mice born without purinergic receptors in the gut display no evident physiological abnormalities (Sun et al., 2001). Yet in tissues of organisms with purinergic receptors, ATP is found to have an activating effect on gut motility and is seen as an important element of signal transduction for the submucosal plexus of guinea pigs (Monro et al., 2004). In pathologies, ATP has been found to be elevated in inflamed regions of the gut, but no studies thus far have found what role ATP plays in gut inflammation (Diezmos et al., 2016). Outside of this, the role of ATP is not well understood in the gut, seemingly because the body is capable of adapting to states in which ATP is imbalanced (Ren and Bertrand, 2008).

γ-AMINOBUTYRIC ACID

The neurotransmitter γ-aminobutyric acid (GABA) is the most known and essential inhibitory neurotransmitter of the CNS. Dysfunctions of GABA transmission and signaling have been implicated in a variety of mental illnesses, including anxiety and depression (Cryan, et al., 2005). Ongoing studies are revealing the complexity of the microbiota in modulating GABAergic signaling in the CNS. In addition, there has been an extensive amount of research that has concluded that GABA mediates the enteric nervous system and therefore, is involved in gastrointestinal function. Contrary to its role within the CNS, GABA is involved in neuronal excitability within the ENS, particularly the GABA-$GABA_A$ receptor system (Seifi et al., 2014). GABA contributes especially to GI motility from the stomach to the ileum as well as peristaltic reflex in the colon (Auteri et al., 2015). Furthermore, $GABA_A$ receptors in particular have been found to mediate inhibition of T cell responses, which would indicate another function of GABA as a natural immunomodulator of T lymphocytes (Tian et al., 1999; Bjurstöm et al., 2008). As a notable enteric immunomodulatory mediator, manipulating GABAergic signaling and GABA receptors have thus been subject to much research interest in their potential to alleviate inflammatory GI diseases, such as IBD. For example, it was found that enhancement of the γ2 subunit of the $GABA_A$ receptor on enteric corticotropin-releasing hormone (CRH) neurons with alprazolam, a benzodiazepine, reversed the increase in force of spontaneous colonic contractions in stress-induced mice (Seifi et al., 2014).

CONCLUSION

The gastrointestinal tract is a complex system that is intricately controlled by several modulators. Local mediators, central nervous system, enteric nervous system as well as hormones produced by other organs all influence catecholamine/serotonin concentrations and its end effect on gut physiology. Furthermore, research shows that this relationship is bi-directional, suggesting that changes in the GI system and enteric nervous system can affect the central nervous system, which is evident in human diseases such as Parkinson's disease. Neurotransmitters namely epinephrine, norepinephrine, serotonin and dopamine, have shown that they play a major role in controlling and maintaining homeostasis within the gut system in terms of nutrient absorption, blood flow, gut microbiome, local immune system, and overall gut motility.

Neurotransmitters play a crucial part in maintaining homeostasis for the entire body. It is understandable that their full functions are not completely understood, because their endogenous concentrations are determined by physiology of the entire human body, making it impossible to isolate the gut. In addition, these catecholamines/serotonin activate different receptors at different concentrations making the picture even more confusing. Even though a vast amount of research is still required, our current working knowledge of catecholamines have already improved patient care; for example, these hormones are used as a last resort to restore blood flow to various organs in times of hemodynamic and septic shock.

The concentration of neurotransmitters is affected in multiple pathological states in which the local concentration can aid and decrease symptomology, secondarily change the gut microbiome, and potentially serve as a biomarker for both GI and CNS pathologies. For example, it is known that both the CNS and gut microbiome plays a significant role in diseases, such as irritable bowel syndrome. In addition, catecholamines and serotonin in the gut can affect both the gut microbiome and the CNS, thus providing a potential therapy method for such diseases. Preliminary research has already shown that they can impact the course of several diseases; further studies are needed to fully evaluate this effect on catecholamines as well as other neurotransmitters and hormones. Understanding molecular mechanisms through which neurotransmitters regulate gut-brain axis will open up avenues to design novel treatment modalities against human diseases.

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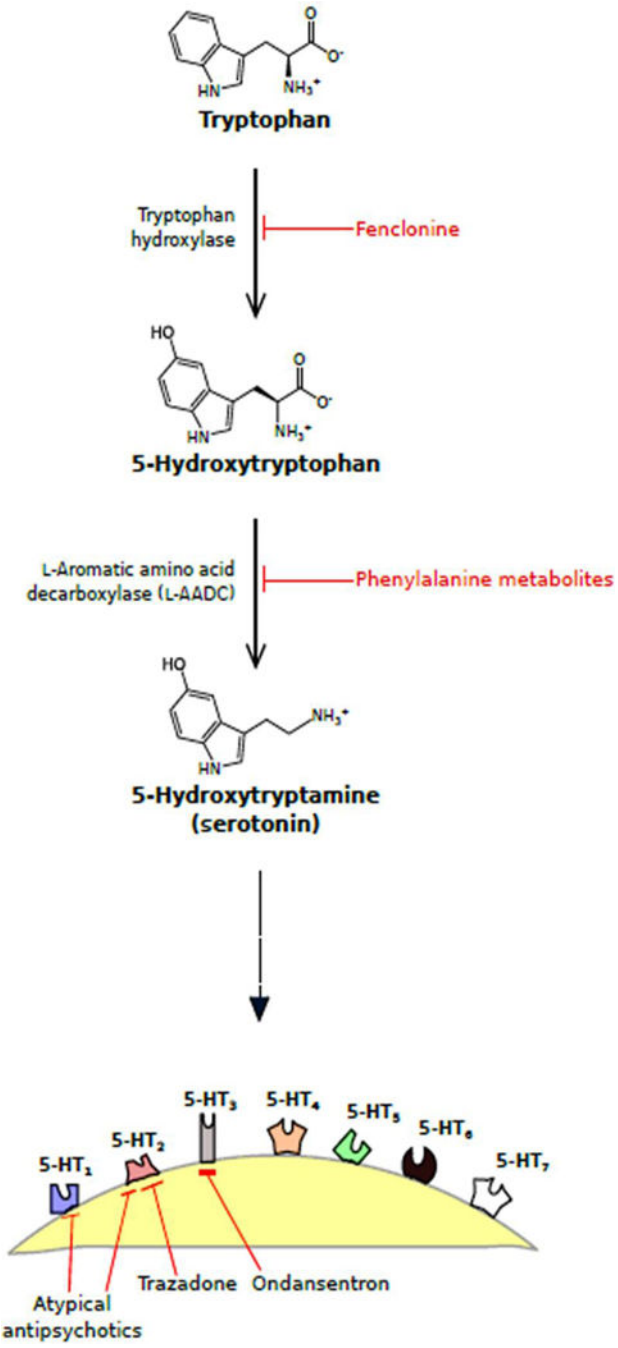

Figure 1. Biochemical pathway for serotonin synthesis with inhibitors of serotonin receptors

Synthesis pathway for serotonin (5-hydroxytryptamine, 5-HT) is depicted here with enzymes responsible for each step as well as known inhibitors of these enzymes. Serotonin will then bind to one of seven 5-HT receptors ($5\text{-HT}_{1\text{-}7}$) at the nerve ending. A few known drug inhibitors of specific 5-HT receptors are also portrayed.

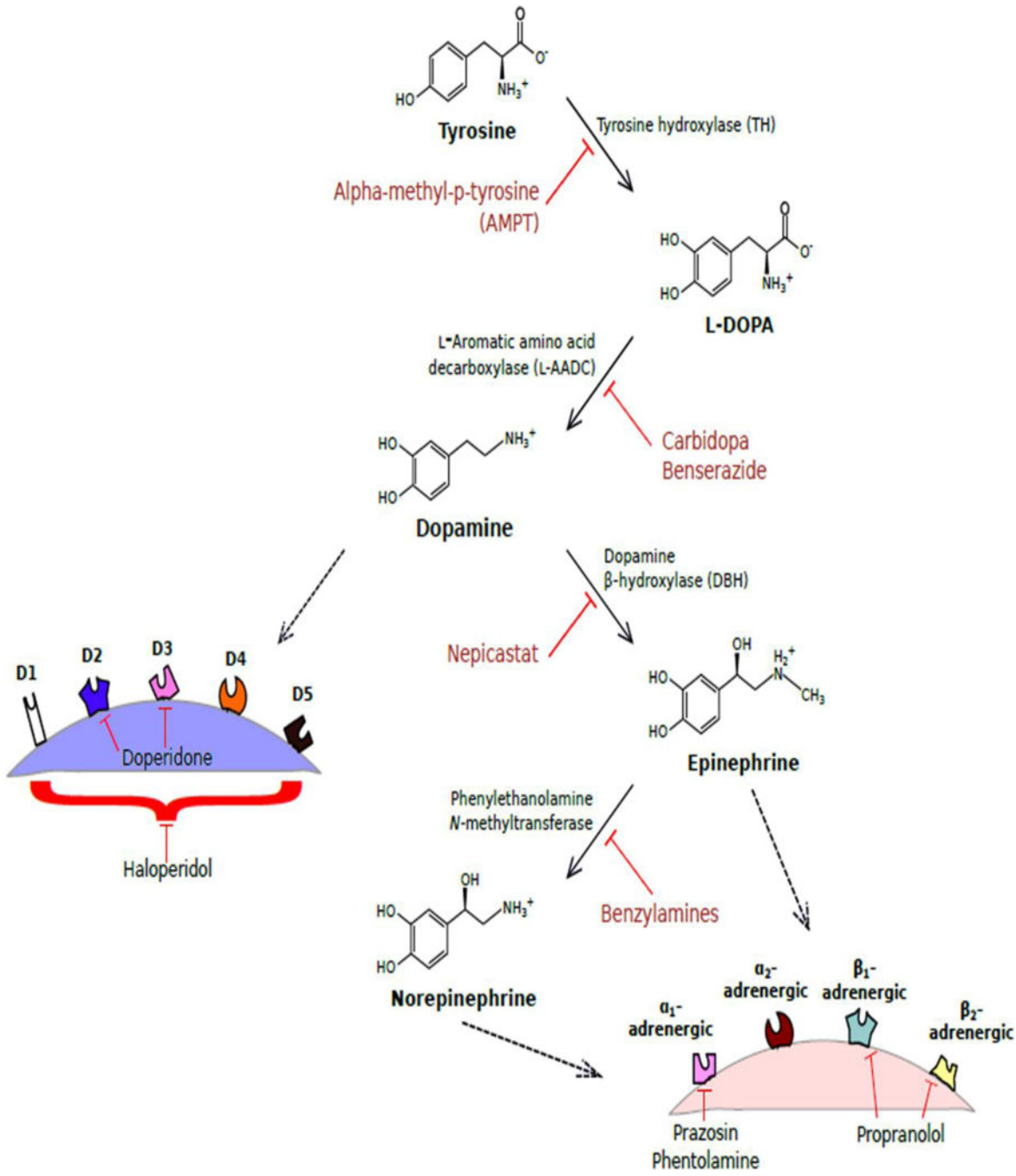

Figure 2. Biochemical pathway for catecholamine synthesis with inhibitors of different dopaminergic and adrenergic receptors

Synthesis pathway for catecholamines dopamine, norepinephrine, and epinephrine are depicted here with enzymes responsible for each step as well as known inhibitors of these enzymes. Dopamine will then bind to one of five dopaminergic receptors (D_1 to D_5) at the nerve ending. Norepinephrine and epinephrine will then bind one of four adrenergic receptors (α1, α2, β1, or β2). A few known drug inhibitors of some of these receptors are also portrayed.

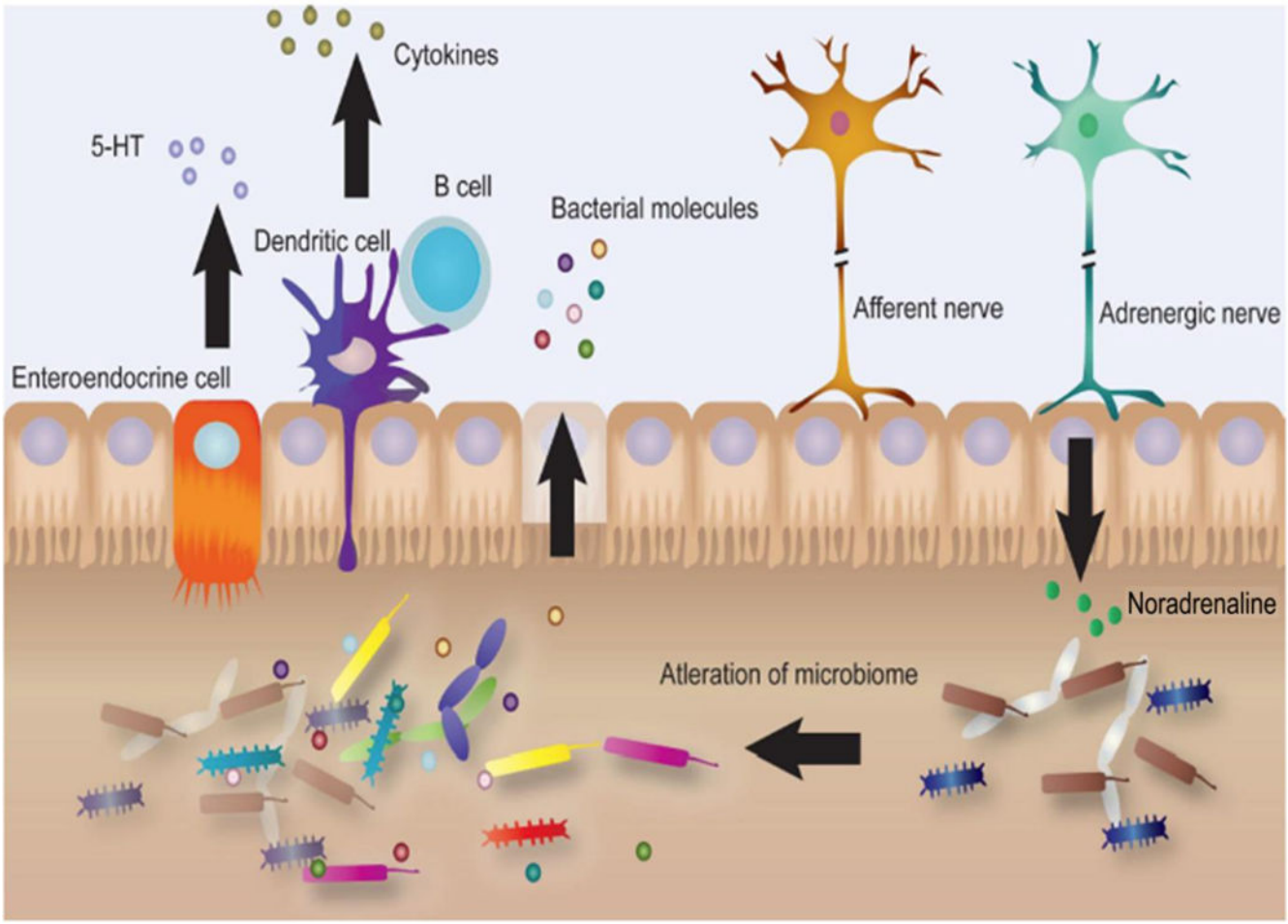

Figure 3. Neurotransmitters affect microbiota in the gut

Neurotransmitters including serotonin alter the microbiota in the gut that can modulate the production of cytokines and bacterial byproducts leading to either heathy or diseased state.

Table 1

Diseases arising from or involved with neurotransmitter dysfunction in the gastrointestinal tract

Summary of diseases for which evidence has linked the pathology to the gut-brain axis. Included is the role played by the neurotransmitter in the pathology, the change in neurotransmitter levels systemically and in the mucosa, and therapies for the pathologies that influence neurotransmitter levels.

Disease/Symptom	Etiology of Disease	Neurotransmitter levels	Neurotransmitter based therapeutic agents	References
Ulcerative colitis	• T-cells aggressively respond to commensal enteric bacteria, resulting in inflammation of the bowel • Differentiated from Crohn's disease because inflammation in ulcerative colitis is continuous and limited to superficial, mucosal layer	• Elevated mucosal 5-HT • Elevated mucosal dopamine • Decreased tissue dopamine • Decreased tissue norepinephrine • Decreased tissue 5-HT	None that target neurotransmitter signaling	Baumgart and Carding, 2007; Sartre, 2006; Coates et al., 2004; Magro et al., 2002
Crohn's disease	• Aggressive t-cell response to commensal enteric bacteria results in inflammation throughout the digestive tract • Differentiated from ulcerative colitis because inflammation is interrupted by healthy tissue and penetrated several layers	• Elevated 5-HT in mucosa and EC cells • Elevated mucosal dopamine • Drastically decreased dopamine • Drastically decreased tissue 5-HT • Depleted mucosal norepinephrine in colon	None that target neurotransmitter signaling	Baumgart and Carding, 2007; Sartre, 2006; Kidd et al., 2009; Magro et al., 2002; Linden et al., 2003
Irritable bowel syndrome	• Discomfort in the bowels caused by irritants, changes in gut microbiota, or susceptibility to inflammation	• Elevated mucosal 5-HT	5-HT_3 receptor antagonists: alosetron or ondansetron 5-HT_4 receptor agonists: lubiprostone or prucalopride 5-HT_4 receptor partial agonist: tegaserod	Camilleri, 2012; Coates et al., 2004; Crowell, 2004
Diverticulitis	• Inflammation in the mucosa of a pouch that has formed in the gut	• Elevated tissue 5-HT in bowel • Decreased mucosal 5-HT in bowel	None that targets neurotransmitter signaling	Costedio et al., 2008; West, 2008; Jeyarajah et al., 2012
Celiac Disease	• Autoimmune disorder of unclear etiology	• It is proposed, but not proven that patients have	None	Di Sabatino et al., 2014

Disease/Symptom	Etiology of Disease	Neurotransmitter levels	Neurotransmitter based therapeutic agents	References
	• Destruction of villi by autoimmune mechanisms results in impaired absorption of nutrients after ingestion of gluten	elevated mucosal 5-HT levels		
Gastro-esophageal reflux disease	• Esophageal sphincter is compromised, resulting in acid refluxing into the esophagus. • Acid in esophagus manifests as chest pain	• 5-HT levels are currently being studied	SRI's and serotonin agonists are being tested for use in restoring the esophageal sphincter	Ostovaneh et al., 2014
Parkinson's disease	• Neurodegenerative disease caused by decreased dopamine levels in the nigrostriatal and mesolimic pathways • Disease manifests through motor deficits, most notably tremors and decreased GI absorptive and motile functions	• Near depletion of dopamine in nigrostriatal and mesolimbic pathways	Deep brain stimulation of the subthalamus results in improvement of GI dysfunction	Sugama and Kakinuma, 2016; Natale et al., 2008; Toti and Travagli, 2014; Singaram et al. 1995; Krygowska-Wajs et al., 2016; Corbillé et al., 2016
Depression	• Neurotransmitter imbalances result in brain alterations that lead to changes including persistent sadness, loss of interest, and decreased energy level	• Decreased 5-HT • Decreased norepinephrine • Decreased dopamine	Agonists and reuptake inhibitors of serotonin, norepinephrine, and dopamine	O'Mahony et al, 2015; Collins et al., 2012;
Anxiety	• The exact mechanism of anxiety is unclear. • It is believed that decreased levels of GABA result in disinhibition of portions of the limbic system. • Anxiety manifests as excessive worry about certain stressful situations	• Elevated Norepinephrine • Decreased GABA	GABA potentiation relieves anxiety. Serotonin increase through SSRI's or tryptophan is shown to relieve symptoms. Corticotropin releasing hormone antagonists decrease anxiety.	Liang et al., 2015; Desbonnet et al., 2015
Autism Spectrum Disorders (ASD)	• The exact mechanism of autism is unclear • It is known that there are size and	Neurotransmitter levels are widely varied and poorly understood in ASD	Cognitive and behavioral therapy	De Angelis et al, 2015; Rosenfeld, 2015; Moos et al., 2016

Disease/Symptom	Etiology of Disease	Neurotransmitter levels	Neurotransmitter based therapeutic agents	References
	activity differences between ASD and non-ASD brains • ASD manifest as a diverse range of social and cognitive deficits			
Esophageal Motility disorders	• Disorders which result in inability to swallow or keep down food due to decreased gut motility	• The exact details of serotonin levels are unknown	Administration of SRI's and serotonin agonists have shown some success in the treatment of esophageal motility disorders	Karamanolis et al., 2015; Scheerens et al., 2015
Hypersensitive esophagus	• Unclear etiology • Decreased threshold for pain in esophagus due to esophageal disruptions caused by chemical or mechanical stress	• The exact details of serotonin levels are unknown	Administration of SRI's and serotonin agonists have shown some success in the treatment of Hypersensitive esophagus in select patients	Dickman et al., 2014; Viazis et al., 2011; Viazis et al., 2012
Gastrointestina l bleed	• Bleeding in the stomach due to ulcers or lesions • Often caused by the bacteria *Helicobacter pylori*	• Elevated serotonin	Care should be taken when administering SRI's to patients with ulcers from *H. pylori*. Aspirin should be avoided in conjunction with SRI's for patients who have ulcers from *H. pylori*, but still must take SRI's	Dall et al., 2011; Wang et al., 2014

Table 2
List of receptors and the molecules that activate them

Summary of the receptors known to be relevant to the gut-brain axis including inhibitors, agonists, and the locations in which the receptors may be found.

Receptor	Inhibitors	Agonists	Location	References
α_1 - adrenoreceptors	• Prazosin • Phentolamine	• Epinephrine • Norepinephrine • Phenylephrine • Methoxamine • Midodrine • Oxymetazoline	• Mesenteric arterioles	Luo et al., 2016, Kim and Jwa, 2015, Manoharan et al., 2016, Hirst and Silinsky, 1975, Grayson and Oyebola, 1983
α_2- adrenoreceptors	N/A	• Epinephrine • Norepinephrine • Clonidine • Oxymetazoline	• Postsynaptic CNS neurons • adrenergic and cholinergic nerve terminals • vascular smooth muscle	Shelkar et al., 2016
β_1-adrenoreceptors	• Propranolol	• Epinephrine • Norepinephrine • Isoprenaline • Dopamine • Dobutamine	• Mesenteric arterioles	Manivasagam et al., 2016, Grayson and Oyebola, 1983
β_2-adrenoreceptors	• Propranolol	• Epinephrine • Isoprenaline • Salbutamol • Albuterol • Terbutaline • Salmeterol • Formoterol • Pirbuterol • Albuterol • Mirabegron	• Mesenteric arterioles	Edgell et al., 2016, Arcaro et al., 2016, Cortese et al., 2016, Blais et al., 2016, Grayson and Oyebola, 1983
D_1	• Haloperidol	• Dopamine • Fenoldopam	• Nerve endings of intestinal wall • mucosal layer	Borcherding et al., 2015, Sclafani, 2001

Receptor	Inhibitors	Agonists	Location	References
D_2	• Haloperidol • Doperidone	• Dopamine • Aripiparazole • Quinpirole • Ketamine • Phencyclidine • Bromocriptine	• Nerve endings of intestinal wall	##Ji and Wu, 2016, Jiang et al., 2016, Li et al., 2015, Lladó-Pelfort et al., 2016, Sclafani, 2001
D_3	• Haloperidol • Doperidone	• Dopamine • Quinpirole • Cariprazine	• Nerve endings of intestinal wall • mucosal layer	Watson et al., 2015, Sander et al., 2016, Sclafani, 2001
D_4	• Haloperidol	• Dopamine	• Mucosal layer	Sclafani, 2001
D_5	• Haloperidol	• Dopamine	• Nerve endings of intestinal wall • mucosal layer	Sclafani, 2001
5 - HT_1	• Atypical Antipsychotics	• Serotonin (5-HT_{1A}) • Azapirones (5-HT_{1A})) • Triptans (5-HT_{1B} and 5-HT_{1D})	• Pre-synaptic enteric nerves • gastrointestinal smooth muscle	Kishi et al., 2013, Araldi et al., 2016, Gershon et al., 1990
5-HT_2	• Trazadone • Atypical Antipsychotics	• LSD (5-HT_{2A}) • Lisuride (5-HT_{2A}) • Mescaline (5-HT_{2A}) • Lorcaserin (5-HT_{2C})	• Gastrointestinal smooth muscle	Karaki et al., 2014, Higgins et al., 2016, Gershon et al., 1990
5-HT_3	• Ondansentron	N/A	• Myenteric neurons	Neal and Bornstein, 2006
5-HT_4	N/A	• Cisapride • Tegaserod	• Myenteric neurons, muscularis mucosa	Lefebvre et al., 2016, Neal and Bornstein, 2006