Alistipes: The influence of a commensal on anxiety and depression

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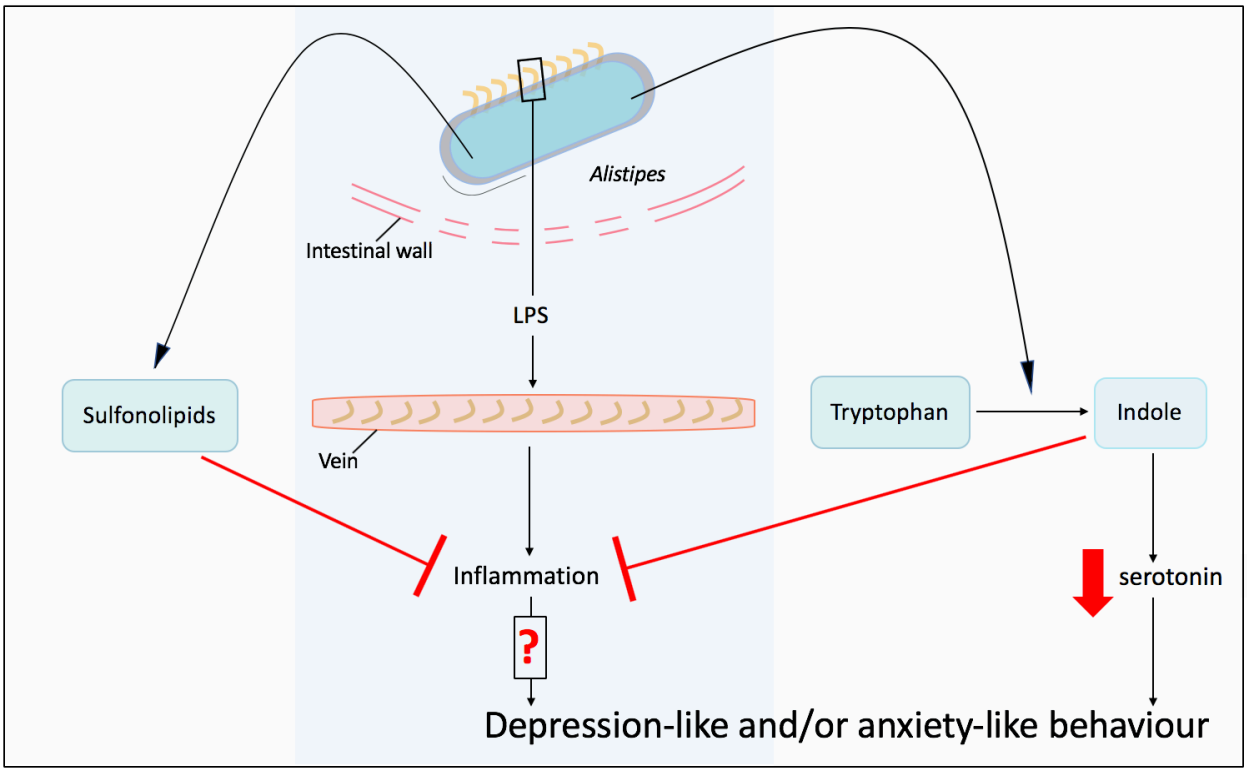

Abstract

The interaction between the gut microbiome and the brain is increasingly recognized as a potential cause for pathophysiology. With a variety of mechanisms for altering host central nervous system (CNS) function, including tryptophan metabolism and releasing modulatory metabolites, the human microbiome is emerging as a target for the development of therapies against disorders such as anxiety and depression. In this review, the gut microbiota and the microbiome-gut-brain axis will be discussed. Then, the mechanisms by which gut microbiota interacts with the CNS with a focus on anxiety and depression will be outlined. Following this, potential mechanisms whereby *Alistipes* may modulate behaviour including the inflammatory, serotonin and secondary metabolites hypotheses are highlighted. Throughout the review conflicting studies involving these pathways are mentioned. Elucidating a mechanism for a clear link between *Alistipes* and anxiety/depression may lead to novel approaches to treat these disorders.

Introduction

The human microbiome constitutes the microbial and gene content of the microorganisms inhabiting our bodies[1]. Although humans only have around 20000 protein coding genes, our microbiota outnumber this by over 100-fold[1,2]. Moreover, most of these microbes live in our gut[3]. Specifically, the gastrointestinal (GI) tract has 10^{13}-10^{14} microorganisms, and over 90% of these microbes belong to the *Bacteroidetes* and *Firmicutes* phyla[1,4]. *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* phyla are present at a lower abundance[4]. These gut microbes are mutualistic and have many important functions such as harvesting nutrients from the diet, synthesizing vitamins, drug metabolism and altering behaviour[1].

Each individual's microbiome is distinct, however there is evidence for a core microbiome shared among individuals for specific body areas[2,3]. Microbiota begins developing shortly after birth and it is dependent on the mode of delivery. For

example, infants delivered vaginally display microbiota similar to their mother's vaginal microbiome and infants born via Caesarean section display microbiota similar to their mother's skin[5]. By approximately 1 year of age, a child's microbiota is comparable to that of an adult and remains stable overtime[2,4]. However, this isn't to say the composition of the microbiome doesn't change at all. Factors such as diet, intake of antibiotics and lifestyle influence the composition of the microbiome[6].

It is also known that changes in the microbiome and its interaction with the body, including the immune and nervous systems, are correlated with disorders such as major depressive disorder (MDD) and generalized anxiety disorder (GAD)[7,8]. For example, *Alistipes* - which is a genus of bacteria under *Bacteroidetes* - is elevated in patients with anxiety and depression[7–9]. This genera of anaerobic, Gram-negative and rod-shaped bacteria are present in a high abundance in the human intestinal tract[9]. Importantly, modifying diet is a low risk option to altering the microbiome that has the potential to function as a personalized therapy for psychiatric disorders[6].

Microbiota-gut-brain axis: how the microbiome interacts with the CNS in anxiety and depression

The bacteria in our GI tract communicate with the central nervous system (CNS) in a complex bidirectional pathway known as the microbiota-gut-brain axis[3,10]. This axis consists of neural, hormonal and immunological branches[3,10]. There are many proposed mechanisms whereby microbiota affect CNS function, and here 7 are discussed in detail.

Mechanism 1: Altering microbial composition

Altered microbial composition can have a wide range of effects on gut-brain signalling. For instance, a recent cross-sectional study comparing the gut microbiota of healthy patients to patients with GAD showed that individuals with GAD have decreased species richness, reduced short-chain fatty acid producing bacteria and an overgrowth of specific bacterial phyla (*Fusobacteria* and *Bacteroidetes*)[8]. Moreover, significant differences in the composition of gut microbes in MDD patients when compared to healthy controls has also been observed[7]. Interestingly, however, Chen *et al.* recently found decreased levels of *Bacteroidetes* in patients with MDD, which opposed the increased abundance of *Bacteroidetes* found in previous studies[7]. This suggests that the relationship between microbiota and disorders is complex. In fact, the relationship may be an interaction of multiple variables such lifestyle and diet - all which should be considered interdependently in future studies. There are many ways to alter microbial composition, some of which can have a beneficial impact on the host such as probiotic and antibiotic administration. Probiotics are organisms that have a beneficial effect on the host and they can alter gut microbial composition through their metabolic by-products, production of toxins and by preventing the colonization of harmful pathogens by competing for dietary substrates and space[4]. For instance, in a study conducted by Bercik *et al.*, it was observed that brain-derived neurotrophic factor (BDNF) levels were reduced in mice infected with *Trichuris muris*, resulting in increased anxiety-like behaviours[11]. However, upon administration of probiotics, BDNF levels were normalized resulting in an effect similar to antidepressant medication on behaviour[11]. Moreover, antibiotics have a drastic effect on microbial composition. Specifically, they alter the richness and diversity of microbiota and it can take up to 4 years post-treatment for the microbial species to return to normal levels[2].

Mechanism 2: Immune activation

Similar to the gut, the immune system also has bidirectional communication with the CNS which allows it to communicate bacterial effects to the nervous system[4]. For example, it is known that treatment with probiotics can dampen anxiety-like and depressive behaviour[12]. However, Ohland *et al.* showed that the treatment of mice lacking interleukin-10 (IL-10, an anti-inflammatory cytokine which normally acts to reduce the immune response) with the probiotic bacteria *Lactobacillus helveticus* did not reduce anxiety-like behaviour when the mice were assessed in the Barnes maze[13]. Contrastingly, when control mice possessing IL-10 were treated with *L. helveticus* they showed decreased anxiety-like behaviour in the Barnes maze[13]. Thus, demonstrating the significance of the immune system in modulating behaviour via the gut-brain

axis. Even more, microbiota can trigger immune activation by stimulating circulating cytokines. This process is amplified with microbial dysbiosis introduced by external factors like antibiotics and probiotics[3,14]. Immune activation is often implicated in psychiatric disorders like depression, as is the case with an increased abundance of proinflammatory cytokines like interleukin-12 and interferon-γ[3]. It is hypothesized that gut microbiota may interact with the immune system in a way that alters gut barrier function which may cause increased gut sensation resulting in anxiety-like and depressive behaviours[14].

Mechanism 3: Vagus nerve

The vagus nerve, cranial nerve 10, has afferent and efferent branches[4]. Vagal afferent neurons relay sensory information from peripheral organs like the gut to the CNS and it is known that this input affects cognition, emotion and behaviour[14]. For example, *Campylobacter jejuni* (a GI pathogen associated with inflammatory bowel disease) acts through vagal pathways to alter behaviour in mice[14]. It is also thought that stimulating vagal pathways reduces anxiety and depression[15]. This comes from a study conducted by Krahl *et al.*, whereby mice exposed to daily vagus nerve stimulation showed increased mobility and antidepressant activity during forced swim testing when compared to control mice[16]. Currently, vagal stimulation is a controversial method used to treat depression that is unresponsive to the available medications[15].

Mechanism 4: Hypothalamic-pituitary-adrenal axis

Microbial colonization affects hypothalamic-pituitary-adrenal axis (HPA) development and responsiveness[17]. The HPA is the endocrine control of the stress system and it mediates the release of corticotropin-releasing factor from the hypothalamus, adrenocorticotropic hormone (ACTH) from the anterior pituitary and cortisol from the adrenal glands during the stress response[4]. Although it is known that microbiota influence HPA development and its response to stress, the reverse relationship is also seen. In fact, cortisol release from the adrenal glands during stressful situations alters gut permeability which can change microbial composition[4]. So, it may be possible to decrease anxiety in patients with GAD by altering microbial composition to alter the HPA. Moreover, the link between microbiota and the HPA was first established when germ-free mice demonstrated increased corticosterone and ACTH levels when compared to specific-pathogen-free mice exposed to stress[17]. Since then it has been shown that the HPA is moulded by early life events. For example, adult animals with maternal deprivation at a young age have an increased HPA response during stressful events when compared to adult animals without maternal deprivation at a young age[17].

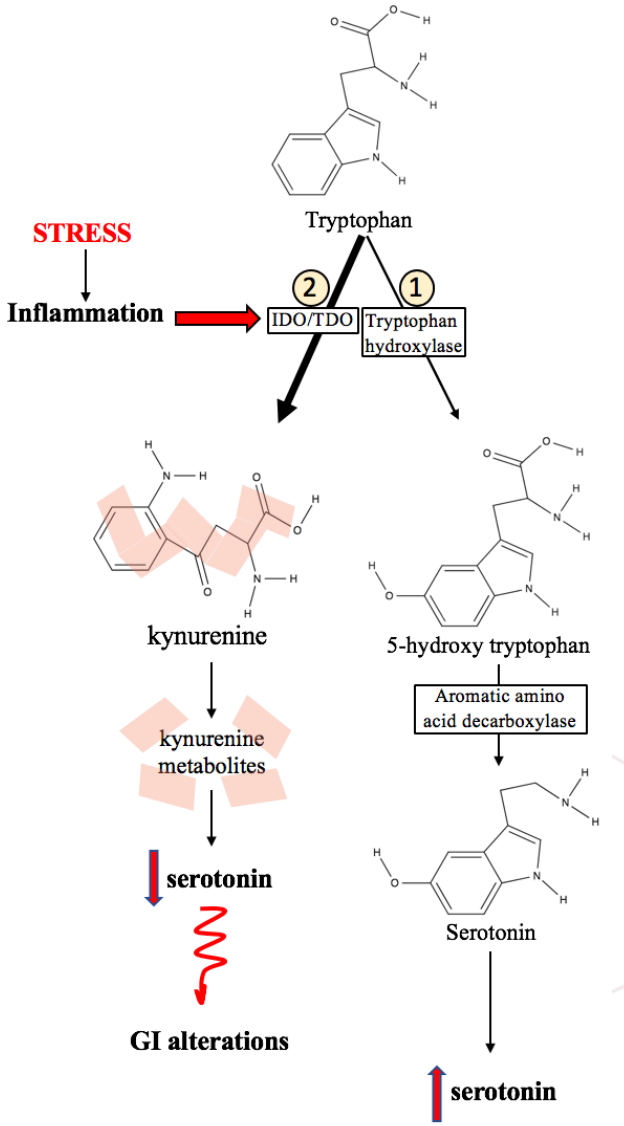

Figure 1. *The two arms of tryptophan metabolism.* The first arm of tryptophan metabolism results in serotonin production through the mechanism depicted above. Dietary tryptophan is converted to 5-hydroxytryptophan by tryptophan hydroxylase, which is then converted to serotonin via aromatic amino acid decarboxylase[10]. The second arm of tryptophan metabolism is the kynurenine arm and it is characterized by the production of

kynurenine (simplified in light orange)[10]. The production of kynurenine and resulting metabolites (simplified as light orange rhombuses) reduces the amount of serotonin available for the host which causes GI alterations.

Mechanism 5: Tryptophan metabolism

Tryptophan (Trp) is an essential amino acid that is obtained from dietary sources[10]. Trp is absorbed through the gut and can enter the circulatory system to cross the blood brain barrier and participate in serotonin synthesis in the CNS[10]. However, over 90% of serotonin is found in the gut where enterochromaffin cells (ECs) of the GI tract convert Trp to serotonin[10,18]. Both in the CNS and the gut, Trp is converted to 5-hydroxytryptophan by tryptophan hydroxylase, which is converted to serotonin via aromatic amino acid decarboxylase (Figure 1)[10]. The kynurenine arm of this pathway is the dominant Trp metabolism pathway and it is dysregulated in many brain and GI disorders[4]. In the kynurenine pathway, kynurenine is produced from Trp by tryptophan-2,3-dioxygenase (TDO) or indolamine-2,3-dioxygenase (IDO) (Figure 1)[10]. This pathway reduces the Trp available for serotonin synthesis and increases metabolites produced by kynurenine which are implicated in psychiatric disorders[3,10].

The serotonergic system is not only implicated in modulating physiological processes like mood and aggression, but it is also implicated in physiological development overall[10]. Moreover, the serotonergic system functions at both sides of the gut-brain axis because serotonin is produced by ECs and in the CNS[10]. Since both gut microbiota and the serotonergic system develop simultaneously, it is plausible that both these systems interact to alter host behaviour[10]. For example, it was previously found that stress causes inflammation which activates IDO and TDO, resulting in decreased Trp and increased kynurenine, which alters GI function (Figure 1)[10]. Even more, germ-free mice reproducibly display increased plasma Trp and exhibit decreased anxiety-like behaviours when compared to microbially colonized mice[10]. Lastly, it is known that certain bacterial strains have tryptophanase enzymes which produce indole from Trp, limiting serotonin production in the host (Figure 2)[10]. It is therefore possible that modifying gut composition could alter kynurenine and indole levels to beneficially modify behaviour[3].

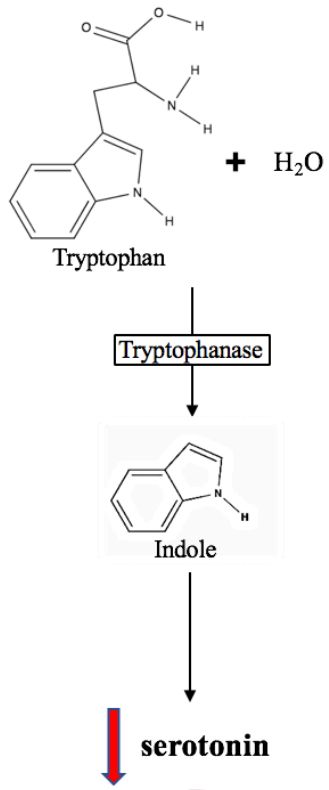

Figure 2. *The production of indole from tryptophan.* Many *Alistipes* species are indole-positive and possess tryptophanase which ultimately disrupts serotonergic balance in the body. It is hypothesized that this property of *Alistipes* may be implicated in anxiety-like and depressive behaviours in individuals[19].

Mechanism 6: Microbial metabolites

Microbial metabolites are the products of the chemical reactions that occur in microbes. There are both primary and secondary metabolites, with the main difference between the two being: primary metabolites are essential for microbial growth whereas secondary metabolites are not[20]. Notably, microbes produce some secondary metabolites that have neuroactive properties during carbohydrate fermentation[4,21]. Such metabolites include: bile acids, choline and short chain fatty acids like L- and D-lactic acid[4,21]. Moreover, it has been shown that increased fermentation results in excess propionate and lactic acid production which causes increased anxiety-like behaviour in mice[21]

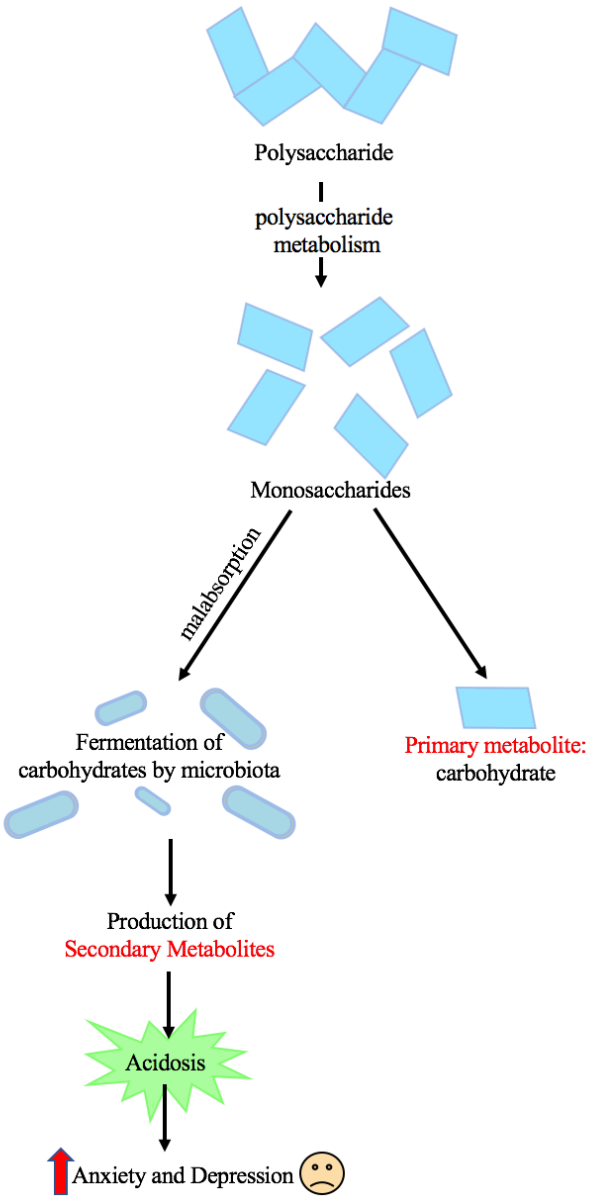

Figure 3. *Depiction of increased anxiety-like and depressive behaviours as a result of carbohydrate malabsorption.* When polysaccharides are broken down to monosaccharides, they are normally absorbed into the gut lumen and stored as primary metabolites. However, in the case of carbohydrate malabsorption, microbiota in the gut (blue rods above) ferment excess carbohydrates and produce secondary metabolites resulting in anxiety-like and depressive behaviour in mice.

Carbohydrate malabsorption also results in a similar effect in humans, whereby malabsorbed carbohydrates are fermented by gut bacteria resulting in high faecal propionic acid and acetic acid concentrations that correlate with negative emotions like anxiety and depression (Figure 3)[22]. This further illustrates how diet can alter conditions like anxiety and depression because a diet higher in carbohydrates will result in more acidosis and therefore increased anxiety-like behaviour[3,21].

Mechanism 7: Microbial neurometabolites

Some microbiota can produce neurotransmitters like GABA, serotonin, catecholamines and histamine[14]. When released, these neurotransmitters interact with epithelial cells in the intestinal lumen to directly alter neural signalling via afferent neurons[4]. These neurometabolites also interact with receptors in the enteric nervous system to affect CNS function[7]. For example, *Lactobacillus* has been shown to produce excess GABA through glutamate metabolism *in vitro* (Figure 4)[23]. This may help reduce anxiety and depression in a manner similar to GABA-like antidepressant and anxiolytic drugs[23].

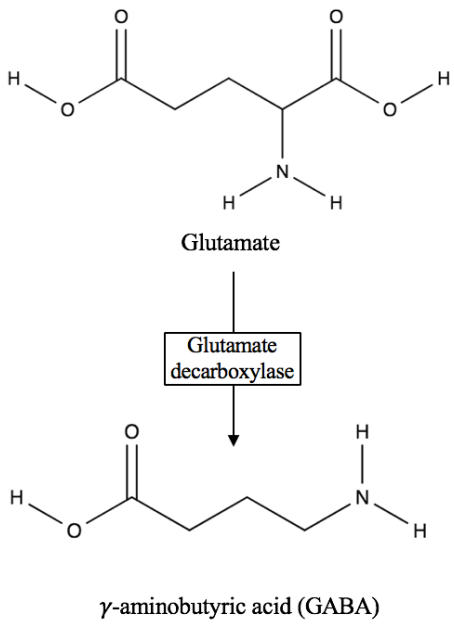

Figure 4. *GABA synthesis from glutamate.* Image adapted from: Production of gaba (γ – Aminobutyric acid) by microorganisms: a review[24]. GABA is a major inhibitory neurotransmitter in the mammalian CNS, and it has hypotensive, tranquilizing effects. It was found that chicken cecal *Alistipes* expresses glutamate decarboxylase which is the enzyme that converts glutamate to GABA as indicated above. It is possible that this may have anti-anxiety and anti-depressive effects on the host due to GABA's role as a potential antidepressant.

Alistipes *and its interaction with anxiety and depression*

It is hypothesized by many different groups that *Alistipes* may cause anxiety-like and depressive behaviours by altering the serotonergic system[25–28]. Although most *Alistipes* test indole-positive and are capable of metabolizing Trp to indole, some species like *A. obesi* and *A. indistinctus* do not produce indole in the presence of Trp[9,29,30]. Therefore, it is possible that not all *Alistipes* species are implicated in anxiety and depression, or there may be multiple mechanisms of action for this interaction. In this review three popular hypothetical mechanisms are discussed in greater detail.

Hypothesis 1: Inflammation hypothesis

Not only are *Alistipes* overexpressed in depressed patients, but they are also associated with the generation of inflammatory molecules that spread into the blood when gut permeability is altered[26,31]. Specifically, *Alistipes* are known to produce lipopolysaccharide (LPS)[32]. LPS is an endotoxin derived from the outer membrane of Gram-negative bacteria[33]. Microbial dysbiosis results in altered intestinal permeability allowing pro-inflammatory molecules like LPS into the bloodstream (Figure 5) [31]. LPS is known to cause systemic and psychiatric changes, otherwise known as sickness behaviour, in mammals[34]. For example, Haba *et al.* demonstrated that LPS injection induces depression-like behaviours 6 and 24 hours after injection in BALB/c mice[34].

Moreover, Qin *et al.* showed that LPS injection in mice increased serum TNF-α which induces pro-inflammatory cytokine production in the brain, serum and liver resulting in prolonged neuroinflammation[33]. The production of inflammatory cytokines in the CNS alters brain activity and modulates the synthesis of neuropeptides, both of which are associated with psychiatric disorders like depression[31]. LPS has also been implicated in increased activity in the emotional centre of the CNS, the amygdala[31]. It has previously been hypothesized that activation of the amygdala for long periods of time underlie depressed exploration in mice[34]. The exact mechanisms by which *Alistipes* participates in increasing inflammation and the resulting depression behaviours observed in mammals is unclear, however the relationship is evident in multiple studies.

Hypothesis 2: Interference with neurotransmitter signalling

Although many different groups, including Inserra *et al.*, found relatively higher levels of *Alistipes* in the gut microbiota of patients experiencing periods of active depression when compared to healthy controls, the role of *Alistipes* in psychiatric disorders is unclear[35]. Many *Alistipes* species are indole-positive and may influence the availability of Trp and therefore disrupt the balance of the serotonergic system[28]. Moreover, it is known that *Alistipes* contain the tryptophanase gene which directly produces indole from Trp (Figure 2), further supporting this hypothesis[19]. However, indole is beneficial and attenuates damage to the GI tract[18]. Contrary to the proposed compromised intestinal permeability and inflammation associated with psychiatric disorders, indole exposure strengthens the mucosal barrier

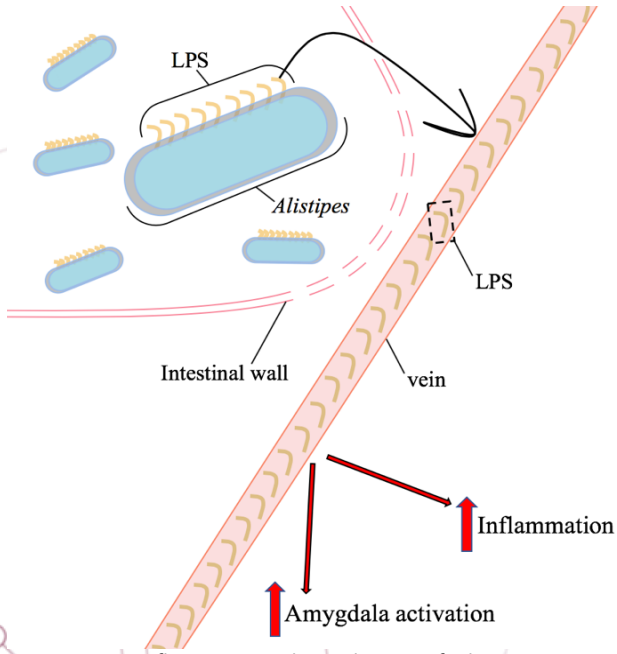

Figure 5. *Inflammation hypothesis of the association between* Alistipes *and depression.* It is hypothesized that when microbial dysbiosis ensues, intestinal permeability is compromised as depicted by the two broken red lines surrounding the *Alistipes*. This altered permeability is thought to allow LPS into circulation and ultimately cause increased inflammation in the liver, CNS and serum[31]. LPS causes prolonged activation of the

amygdala in mice which results in depressed exploration[34].

and suppresses pro-inflammatory cytokine production[18]. Therefore, it is possible that *Alistipes*, although elevated in GAD and MDD, confers a beneficial effect to the host. On the other hand, van Beek *et al*. found that *Alistipes* are associated with IDO overexpression[36]. IDO is an enzyme in the kynurenine pathway which produces Trp metabolites that are implicated in psychiatric disorders (Figure 1)[10,36]. However, van Beek *et al*. stated there is no evidence for a relationship between the abundance of *Alistipes* and altered Trp metabolism[36]. As a result, the intriguing hypothesis of *Alistipes* altering the serotonergic system to cause disorders like anxiety and depression requires further investigation as there is a possibility that this association is either insignificant or beneficial for the host.

Hypothesis 3: Natural products – secondary metabolites

Natural products are produced by organisms and include both primary and secondary metabolites. *Alistipes* are involved in the production of two interesting secondary metabolites. First, Walker *et al*. found that mice fed high-fat diets produce sulfonolipids (SLs) which are a unique type of sphingolipid produced exclusively by *Alistipes* and *Odoribacter*[37]. SLs have previously been described to have anti-inflammatory effects, and in this study sulfobacin B (the specific SL produced by *Alistipes*) suppressed the activation of the proinflammatory cytokine TNF-**α**[37]. Interestingly, LPS is found in the cell wall of *Alistipes* and has the potential to activate TNF-**α** which may cause inflammation[33]. The opposing outcomes of LPS and SLs raise the question of whether *Alistipes* actually contributes to the inflammation associated with psychiatric disorders, or whether it has a beneficial or neutral effect in the host.

Additionally, Polanksy *et al*. found that *Alistipes* expressed glutamate decarboxylase which produces **ɣ**-aminobutyric acid (GABA) from glutamate in chicken cecal microbiota (Figure 4) [38]. Although many studies correlate an increased abundance of *Alistipes* with depression and anxiety, this was a very unusual finding since GABA relieves anxiety[7,8,31,35]. However, it is possible that although *Alistipes* can produce GABA, the neurotransmitter may not be released into circulation[38]. Therefore, further investigation of *Alistipes'* ability to produce GABA and the release of this neurotransmitter in the gut lumen is required to elucidate a potential beneficial effect of *Alistipes* for individuals with anxiety and depression.

Discussion

There is an increasing body of research that supports the role of microbial dysbiosis in psychiatric-related illnesses. However, a clear understanding of the mechanisms of action for over and under expressed microbes in these conditions is required. Specifically, many studies have concluded that there is an increased abundance of *Alistipes* in individuals with anxiety and depression. However, it is unclear whether *Alistipes* have a negative or positive impact on these illnesses because some metabolites that it produces, such as indole, GABA and sulfobacin B may alleviate anxious and depressive behaviours. However other products like LPS and kynurenine metabolites may aggravate these behaviours. Moreover, further work is required to clarify the link between the different *Alistipes* species in both the inflammatory and serotonin pathways.

In the future it is important to work towards developing a comprehensive library of *Alistipes* species. With this library *in vivo* assays using animal models like *Caenorhabditis elegans*, *Drosophila* and *Danio rerio*, all of which show conservation in the genes associated with increased risk of mental illness, can be conducted to elucidate the role of *Alistipes* in psychiatric disorders[39]. Moreover, by conducting whole genome sequencing of all the isolated *Alistipes*, the sequences can be compared to those found in other organisms to identify conserved genes that may be associated with psychiatric disorders. For example, if it is found that human *Alistipes* from the gut of healthy patients all express glutamate decarboxylase as seen in chicken cecal microbiota, it may be possible that *Alistipes* exerts a beneficial effect on these individuals by lowering their risk of developing anxiety-like or depressive behaviours. Lastly, elucidating the

mechanism by which *Alistipes* communicate with the gut-brain axis is pivotal to developing personalized microbiota-based and microbiota-specific therapies to treat anxiety and depression.

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