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REVIEW PAPER

Actions of Trace Amines in the Brain-Gut-Microbiome Axis via Trace Amine-Associated Receptor-1 (TAAR1)

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Abstract

Trace amines and their primary receptor, Trace Amine-Associated Receptor-1 (TAAR1) are widely studied for their involvement in the pathogenesis of neuropsychiatric disorders despite being found in the gastrointestinal tract at physiological levels. With the emergence of the "brain-gut-microbiome axis," we take the opportunity to review what is known about trace amines in the brain, the defined sources of trace amines in the gut, and emerging understandings on the levels of trace amines in various gastrointestinal disorders. Similarly, we discuss localization of TAAR1 expression in the gut, novel findings that TAAR1 may be implicated in inflammatory bowel diseases, and the reported comorbidities of neuropsychiatric disorders and gastrointestinal disorders. With the emergence of TAAR1 specific compounds as next-generation therapeutics for schizophrenia (Roche) and Parkinson's related psychoses (Sunovion), we hypothesize a therapeutic benefit of these compounds in clinical trials in the brain-gut-microbiome axis, as well as a potential for thoughtful manipulation of the brain-gut-microbiome axis to modulate symptoms of neuropsychiatric disease.

Keywords Trace amines · Microbiome · "Gut-brain-axis"

Introduction

The brain-gut-microbiome axis is an emerging area of research highlighting the involvement of gastrointestinal microbes with the comorbidities of several neuropsychiatric disorders. The intestinal tract harbors the most abundant ecosystem of bacteria with concentrations ranging from 10^3 to 10^{14} bacteria depending on tissue localization (Hillman et al. 2017). The idea that microbes have a beneficial impact on human health predates our current understanding of the microbiome by 100 years, as E. Metchnikoff associated fermented food products with longevity in a rural population, and suggested that lactobacilli could counteract the effects of illness and aging (Metchnikoff and Mitchell 1908). In 2007, the United States National Institutes of Health established the "Human Microbiome Project" to improve the understanding of the microbial flora in human health. The collective genome of the microbial species living on our body, termed metagenome, outnumbers the human genome by a factor of 200 (Qin et al. 2010; Ray et al. 2019). Thus, it is not surprising that the metagenome and its encoded metabolic activities play a crucial role in all aspects of human health and disease (Marcobal et al. 2012). As such there has been a focus on the role of bacterial metabolic byproducts in human health (Jacobs et al. 2016; Santoru et al. 2017; Smith and Macfarlane 1997; Vandenberg et al. 2003; Kisuse et al. 2018). Meanwhile, advances have been made in animal studies using germ-free mice, suggesting that disturbances

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in the intestinal microbial flora can alter brain chemistry and behavior (Park et al. 2013). About 60% of anxiety and depression patients are described to have intestinal function disturbance, such as in irritable bowel syndrome (Gupta et al. 1997). Recently, irritable bowel syndrome has also been related to changes in intestinal microbiota, including disruption of the intestinal microflora. While there has been a focus on the role of complex carbohydrates and neuroactive short-chain fatty acids (e.g. butyrate, acetate and propionate) in the brain-gut-microbiome axis, some of these same studies provide evidence that trace amine levels are altered in gastrointestinal disorders and neuropsychiatric disorders. Here, we propose the novel hypothesis, that the putative trace amine receptor, Trace Amine-Associated Receptor-1 (TAAR1) can augment gastrointestinal illness and neuropsychiatric disorders as a result of a dysregulated intestinal microbial flora. This review discusses several elements of the brain-gut-microbiome axis as it relates to trace amines, TAAR1, and the role they may play in both neuropsychiatric and comorbid gastrointestinal disorders.

TAAR1 is a G protein-coupled receptor that was deorphanized in 2001 (Borowsky et al. 2001; Bunzow et al. 2001) and has been widely studied as a major regulator of dopamine in neuropsychiatric disorders and in acute and neuroadaptive responses to drugs of abuse; and extensively reviewed (Berry et al. 2017; Christian and Berry 2018; Grandy et al. 2016; Schwartz et al. 2018). Currently, specific TAAR1 compounds are nearing completion of clinical trials for treatment of schizophrenia and Parkinson's related psychoses (Roche, Sunovion). The predominant endogenous ligands for TAAR1 are classified as 'trace amines' and include p-tyramine, β-phenylethylamine, tryptamine, 3-iodothyronamine, and octopamine as well as 'classical' monoamine neurotransmitters including histamine, serotonin, and dopamine (Borowsky et al. 2001; Chiellini et al. 2012; Hoefig et al. 2015; Pugin et al. 2017; Sotnikova et al. 2010; van Kessel et al. 2019). Trace amines activate TAAR1 at nanomolar affinities, whereas classical monoamine neurotransmitters activate the receptor at or near micromolar concentrations (Panas et al. 2012; Xie et al. 2007).

The term trace amine was adopted by a study group at the 1975 meeting of the American College of Neuropsychopharmacology (Usdin and Sandler 1976), and it is now often mentioned that the levels of trace amines are < 10 ng/g (Berry 2004; Gainetdinov et al. 2018). trace amines are classically defined as any monoamine with a physiological level less than 1–100 ng/g of tissue weight (Boulton 1974) though oftentimes higher levels are subsequently identified in new tissue assessments of particular amines. Historical studies of trace amines in the body have correlated imbalances in trace amine levels to neuropsychiatric disorders including schizophrenia, substance abuse, depression, attention-deficit hyperactive disorder, and Parkinson's, and has been extensively reviewed (e.g. Gainetdinov et al. 2018). A role of trace amines in the gut has not been systematically studied, likely because the identification of trace amines and their hypothesized role in neuropsychiatric disorders was decades before the understanding of the microbiome and metabolome. Perhaps because of the focus of trace amines in psychiatric illness over prior decades, the discovery of TAAR1 in 2001 led to a body of research studying the effects of TAAR1 in modulating monoaminergic signaling in the brain. The proposed and known functions of TAAR1 in neuropsychiatric disorders have been extensively reviewed and as such will only be briefly described here when relevant.

Recent research has increasingly drawn connections between perturbations to the gut microbiota and both gastrointestinal and psychiatric conditions (Felice and O'mahony 2017). The gastrointestinal tract is a heterogeneous layer of tissue comprised of smooth muscle, neuronal cells, immune cells, and epithelial cells. Maintenance of gastrointestinal homeostasis is dynamic and involves the regulation of the epithelial cell monolayer to protect the underlying immune cells and neurons to prevent excessive inflammation (Rao and Wang 2010). There are billions of neurons interconnected via trillions of synapses in the gut and brain, all of which are primarily governed by communication mediated by neuromodulators. One way these modulators are hypothesized to link the gut and brain is by production of aminergic compounds from the gut microbiota—a diverse collection of microbial communities that are thought to influence a wide array of biological processes. Within the realm of neuromodulators originating from the microbiota exist the trace amines (Pugin et al. 2017). Several enteric and food-borne microorganisms are known to produce tyramine and β-phenylethylamine, as listed in Table 1. In fact, around 3 g of un-degraded proteins and peptides enter the human intestine every day from diet, as well as from endogenous sources such as host tissues, pancreatic enzymes and other secretions (Chacko and Cummings 1988). Such large amounts of organic nitrogen-containing compounds are available for catabolism to amino acids, providing essential amino acids to the host (e.g. phenylalanine) and further metabolic degradation by intestinal microorganisms (Fig. 1a) (Rasnik et al. 2017). It has been suggested that in response to an acidification of the environment, microorganisms, such as those listed in Table 1, upregulate several transporters including the tyrosine transporter and a tyrosine decarboxylase (Wolken et al. 2006). Once transported intracellularly, tyrosine is rapidly decarboxylated to tyramine by the bacterial tyrosine decarboxylase (TyrDC), where it is then exported from the microorganism by the tyrosine transporter (TyrP), mechanistically described in Fig. 1b (Wolken et al. 2006). When produced in adequate amounts, gut bacterial-produced trace amines have been shown to have differing effects for the host. For example, β-phenylethylamine is reported as an

Table 1 Enteric and/or food-borne bacterial species able to synthesize trace amines and subsequent levels in the gastrointestinal tract

Trace amine	Trace amine concentrations in or transiting human gut	Trace amine-producing enteric/food-borne microbes	References
Tyramine	400–750 (mg/L) Pugin et al. (2017)	*A. haemolyticus, A. hydrophila, A. faecalis, B. cereus, B. subtilis C. braaki, C. freundii, C. gallinarum, C. piscicola, C. maltaromaticum, C. divergens, C. freundii, E. faecalis, E. faecium, Enterococcus* sp., *E. coli, E.durans, E. hirae, E. casseliflavus, E. mundtii, E. aerogenes, E. cloacae, K. pneumoniae, L. brevis, Lactobacillus* sp., *L. curvatus, L. plantarum, L. buchneri, L.casei, L. paracasei, L. reuteri, L. hilgardii, L. homohiochii, L. delbruecki, L. lactis, L. alimentarius, L.curvatus, L. mesenteroides, M. morganii, P. mirabilis, P. vulgaris, P. aerugina, R. ornithinolytica, S. thermophilus, S. faecalis, S. macedonicus, Sporolactobacillus* sp., *T. halophilus, W. cibaria, W. confusa, W. paramesenteroides, W. viridiscens*	Barbieri et al. (2019), Bonnin-Jusserand et al. (2012), Borresen et al. (1989), Buňková et al. (2009), Coton and Coton (2009), Coton et al. (2004), Coton et al. (2011), La Gioia et al. (2011), Ladero et al. (2012), Ladero et al. (2013), Leisner et al. (2007), Linares et al. (2011), Maifreni et al. (2013), Marcobal et al. (2012), Marcobal et al. (2006), Min et al. (2004), Moreno-Arribas et al. (2001), Pessione et al. (2005), Pessione et al. (2009), Pircher et al. (2007), Pugin et al. (2017), van Kessel et al. (2019) and Zhu et al. (2016)
β-Phenylethylamine	10 nmol/g Turroni et al. (2016)	*B. cereus, C. divergens, C. carnosus, E. faecium, E. faecalis, E. casseliflavus, E. durans, E. mundtii, E. hirae, L. lactis, L. brevis, L. mesenteroides, Staphylococcus* sp., *P. aerugina*	Bargossi et al. (2015), de Las Rivas et al. (2008), Landete et al. (2005), Linares et al. (2011), Min et al. (2004), Perin et al. (2017) and Pessione et al. (2009)

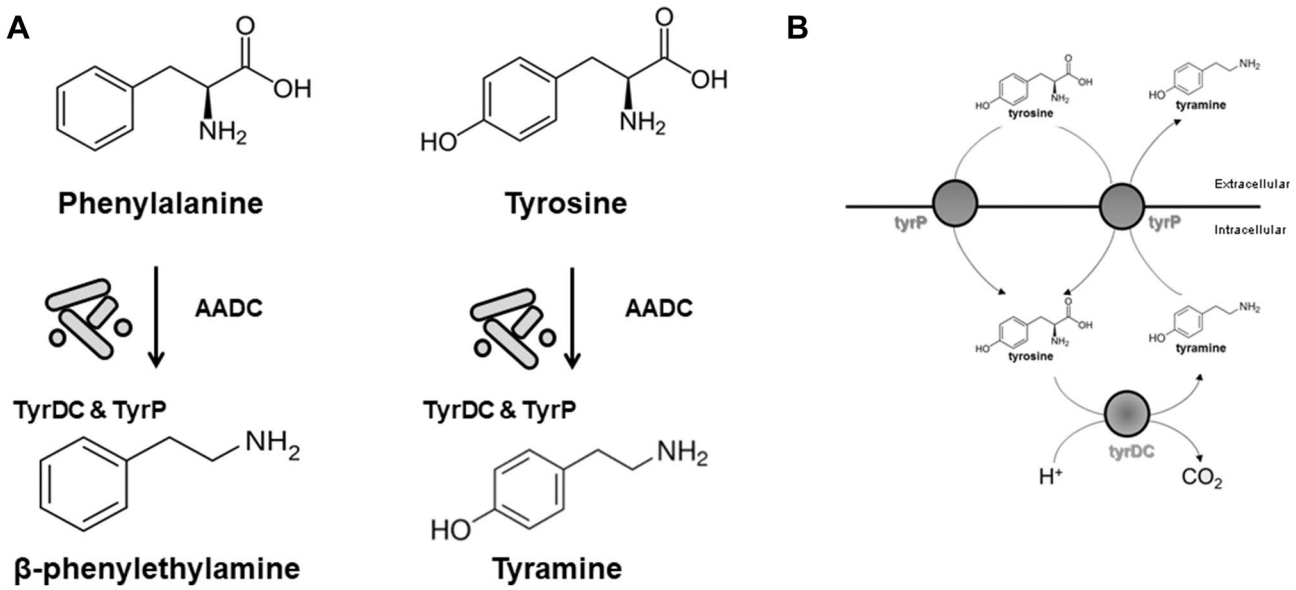

Fig. 1 **a** 2 Metabolic byproducts of dietary amino acid metabolism by mammalian and microbial enzymatic systems. Phenylalanine and tyrosine are decarboxylated by the microbial TyrDC & TyrP system and mammalian aromatic amino acid decarboxylases (AADC) to phenylethylamine and tyramine respectively. **b** Microbial transport and decarboxylation of tyrosine. Tyrosine is taken in by the tyrosine transporter (tyrP) into microbes where the enzymatic decarboxylation of tyrosine to tyramine occurs by the tyrosine decarboxylase (TyrDC) enzyme. Tyramine is then transported to the extracellular space of the microbe by tyrP (Bargossi et al. 2017; Bargossi et al. 2015; Pessione et al. 2009; Wolken et al. 2006). A similar mechanism occurs for decarboxylation of phenylalanine to β-phenylethylamine by tyrosine decarboxylase

antimicrobial against pathogenic *E. coli* (Lynnes et al. 2014), and tyramine has been shown to stimulate fast ileal contractions and neuropeptide Y release (Broadley et al. 2009), as well as increasing synthesis and secretion into circulation of monoamine neurotransmitters (Yano et al. 2015). Modulation of intestinal motility and secretion can have profound effects on luminal pH, mucosal immune response, and delivery of important nutrients to the host cells and enteric microbiota.

TAAR1 localization has been identified in both the stomach and the intestine in mouse and human (Chiellini et al. 2012; Adriaenssens et al. 2015; Ito et al. 2009; Kidd et al. 2008; Ohta et al. 2017; Raab et al. 2015; Revel et al. 2013), but the exact function in the polarized gastrointestinal epithelium remains largely unexplored. Here, it is worth noting that despite no definitive function being identified in the polarized epithelium of the stomach and intestine, TAAR1 functionality has been described in the beta-cells of the pancreas, co-localized with PYY and GLP-1 in duodenal cells, and selective TAAR1 agonists resulted in elevated plasma levels of PYY and GLP-1 (Raab et al. 2015), though these studies are not relevant to our discussion the brain-gut-microbiome axis. Functional TAAR1 was found in almost all peripheral immune cells (Babusyte et al. 2013; Panas et al. 2012; Sriram et al. 2016; Wasik et al. 2012), with evidence that TAAR1 can modulate not only intracellular signaling (Panas et al. 2012), but also immune cell functions such as chemotaxis (Babusyte et al. 2013), phagocytosis [unpublished abstract, Miller Lab (Gwilt et al. 2018)] and altered expression of cytokines (Bugda Gwilt et al. 2019a; Babusyte et al. 2013). Immune cells are known to infiltrate the gastrointestinal tract with epithelial damage and inflammation, and given the reported chemotactic capacity of TAAR1 positive cells towards trace amines, TAAR1 positive immune cells should be noted in the gastrointestinal microenvironment given the propensity of patients with neuropsychiatric disorders to also present with peripheral inflammation.

Our lab has identified TAAR1 expression in the gastrointestinal tract of C57BL/6 mice, summarized in Fig. 2 (Bugda Gwilt et al. 2019b; Ito et al. 2009), in human intestinal epithelial cell lines (unpublished data), as well as enteric glia (Fig. 2c). Interestingly, TAAR1 localization is primarily intracellularly in colonic epithelium (Fig. 2a) whereas in the small intestine it is predominantly found on epithelial membranes (Fig. 2b). The dynamic expression and localization of TAAR1 has been previously described (Bugda Gwilt et al. 2019a; Sriram et al. 2016; Stavrou et al. 2018) and the production of trace amines by several species in the microbiome (e.g. Bargossi et al. 2015; Pessione et al. 2009; van Kessel et al. 2019) may account for the predominant membranous localization of TAAR1 compared to colonic tissue. In the brain-gut-microbiome axis, gut microbes are able to signal by the vagal nerve, mediating behavioral effects in animals (Forsythe et al. 2014). While vagal nerve signaling is demonstrated to have roles in these effects, studies are lacking that investigate the role of non-neuronal-like tissues in the brain-gut-microbiome axis. Given evidence for the localization of TAAR1 in the gastrointestinal epithelium (Fig. 2a), enteric glia (Fig. 2c) and all peripheral immune cells, it is important to understand the role that these tissues have in mediating gut health and modulation of inflammation by the varied sources of trace amines in the gut. Perhaps, TAAR1 activation in these tissues can be damaging, exposing the sensitive underlying tissue to pathogenic microbes, providing a mechanism of exposure of the vagal nerve pathways to microorganism, or food byproducts.

In addition to bacterial origins, another prominent source of trace amines in the human body is through consumption of fermented food like cheese, pickles, and wine, where the lactic acid bacteria are responsible for production of trace amines in these food products (Marcobal et al. 2012). While the entire Lactobacillus species are considered producers of tyramine (Pessione et al. 2009), only specific Lactobacillus species are found in food products, and some have been found to survive transit through the gastrointestinal tract (Pugin et al. 2017). Bacterial jejunal contents were found to coincide with production of tyramine in the presence of tyrosine decarboxylase ex vivo (Fernandez De Palencia et al. 2011; Van Kessel et al. 2019). When fermented food products are ingested, levels of trace amines in the gut can be raised to undesirable levels (Pugin et al. 2017). As previously discussed, acidification of an environment enriches tyramine production through the TyrP and TyrDC enzymatic systems. Accordingly, tyramine production by Enterococcus species in food is enhanced by lowered pH in the small intestine that can not only simulate rapid passage through the gastrointestinal tract (Fernandez de Palencia et al. 2011), but is common in patients with inflammatory bowel disease (Press et al. 1998).

Dietary trace amines were first described as having a physiological relevance with the advent of a new class of antidepressants: the monoamine oxidase inhibitors. This phenomenon –known as "The Cheese Effect"—has been attributed to accumulation of very high levels of tyramine and β-phenylethylamine in patients being treated with monoamine oxidase inhibitors (Anderson et al. 1993; Price and Smith 1971; Shalaby 1996; Stratton et al. 1991). Patients suffer from severe vasoconstriction as a result of accumulation of very high levels of consumed and bacterial-produced tyramine and phenylethylamine (Anderson et al. 1993; Price and Smith 1971; Shalaby 1996; Stratton et al. 1991). Though the mechanism of the so-called "cheese effect" is not mediated by TAAR1, a similar decrease in monoamine oxidase activity may be present in patients with gastrointestinal illness. A hallmark of several gastrointestinal diseases leads to an ablation of the polarized epithelium, commonly seen

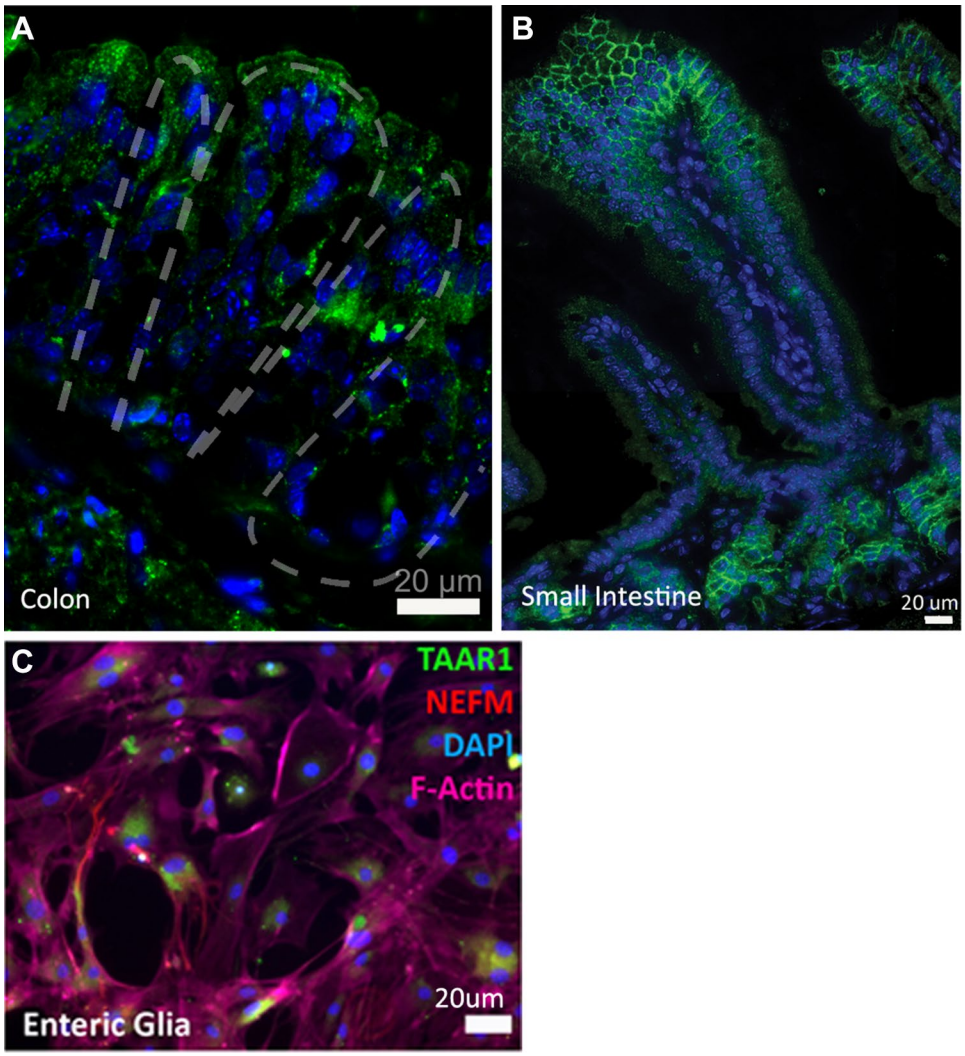

Fig. 2 Summary of TAAR1 expression in mouse gastrointestinal tissue Formalin fixed paraffin embedded mouse tissue (**a**, **b**) was stained with specific TAAR1 antibody, "D274" designed and published by the Miller lab (Bugda Gwilt et al. 2019a). **a** TAAR1 localization is seen in apical epithelial cells and is both intracellularly and membrane localized in colon tissue. Colon tissue morphology is as expected, and crypts shapes are depicted by dashed lines for clarity. **b** TAAR1 localization is seen primarily on membranes of the villus (finger-like projections) and in the base of the crypts. **c** Ex vivo isolated enteric glial cultures were stained with TAAR1 (green) neurofilament medium (NEFM Red), Actin (pink) and DAPI (blue), demonstrating profound intracellular localization of TAAR1 in ex vivo enteric glial cultures

in inflammatory bowel diseases, or an altered microbial composition. In either case, it is reasonable to predict that monoamine oxidase enzymatic activity can be affected by an overabundance of aminergic compounds, or an ablation of the cells harboring the enzyme.

Interestingly, fecal metabolomic studies have identified a higher relative abundance of the TyrDC gene and its harboring bacteria *Enterococcus* in Parkinson's disease patients who require higher frequency of the levodopa daily dosage regime compared to other Parkinson's disease patients (van Kessel et al. 2019). TyrDC has the capacity to decarboxylate levodopa into dopamine, which coincides with the conversion of tyrosine into tyramine (van Kessel et al. 2019). Tyramine has been recently been suggested as an early stage biomarker for Parkinson's due to increased urine tyramine compared to healthy controls (D'andrea et al. 2019). Thus, higher availability of tyrosine or TyrDC in the intestinal tract of those patients may result in accumulation of tyramine, causing detrimental side effects. For example: many patients experience dyskinesias, which have been previously correlated with modulation of the β-arrestin 2 signaling pathway, a pathway that has been previously linked to TAAR1 signaling (Espinoza et al. 2015; Harmeier et al. 2015; Urs et al. 2015).

Tyramine has additional known functions in human intestinal epithelial cell lines (Del Rio et al. 2017), though there are currently no published functional links to a receptor-mediated mechanism by TAAR1 in these epithelial cell models. Briefly—tyramine transiting the gut, presumably from consumption of tyramine rich food—can promote the adherence of microbes to the intestinal epithelial cells (Fernandez De Palencia et al. 2011; Luqman et al. 2018) and can modulate inflammatory cytokine signaling in intestinal epithelial cells (Fernandez de Palencia et al. 2011). Tyramine can also increase the synthesis of serotonin by enteroendocrine cells in the gut, elevating its release into circulation (Yano et al. 2015). Additionally, work from our lab has demonstrated that tyramine activation of bone marrow

derived macrophages from C57BL/6 mice augments secretion of inflammatory cytokine gene expression, an effect that is attenuated by the specific TAAR1 antagonist EPPTB (Bugda Gwilt et al. 2019a). Based on reports that dietary trace amines can activate human TAAR1 in primary epithelial cells (Ohta et al. 2017), these specific effects of tyramine in in vitro human epithelial cell models may be attributed to a specific receptor-mediated mechanism by TAAR1 activation. Our ongoing work is currently seeking to delineate this effect.

Both mouse studies and human patients present with elevated tyramine levels compared to healthy controls in gastrointestinal diseases with comorbid neuropsychiatric disorders including: celiac disease (De Angelis et al. 2016; Di Cagno et al. 2011), colorectal cancer (Goedert et al. 2014; Sinha et al. 2016) and inflammatory bowel disease (Santoru et al. 2017; Nagao-Kitamoto et al. 2016). Metabolomic studies have also identified a role of β-phenylethylamine in the fecal metabolome, and altered phenylalanine metabolism in inflammatory bowel disease (Kolho et al. 2017; Paley 2019; Santoru et al. 2017; Yuan et al. 2018). In a human cohort, the fat composition of the diet can mediate the levels of β-phenylethylamine in the fecal metabolome (Kisuse et al. 2018). No receptor-mediated mechanism has been confirmed for either tyramine or β-phenylethylamine to act on the polarized epithelia of the gut, though a recent review by Christian et al. suggests that TAAR1 may mediate some effects in inflammatory bowel diseases (Christian and Berry 2018).

Trace amines from dietary or microbial synthetic pathways have many potential fates in the gut, some of which may be context specific. In the brain, trace amines are rapidly degraded by tissue monoamine oxidases of neurons and supportive cells, although production and circulation in the brain may provide a more limited source of amines than the plentiful sources in the gut. On a cellular level, trace amines can be absorbed by simple diffusion (Berry et al. 2013; Blakeley and Nicol 1978; Tchercansky et al. 1994), facilitated diffusion (Blakeley and Nicol 1978) or by specific monoamine transporters (Xie and Miller 2008). In vitro studies investigating the small intestine epithelial cell line report β-phenylethylamine absorption to be pH dependent, and showing minimal degradation of luminal β-phenylethylamine by intestinal bacteria (Fischer et al. 2010). Similarly, Tchercansky et al. (1994) showed tyramine is absorbed by rat small intestine epithelium by simple diffusion (Tchercansky et al. 1994), and tyramine plasma levels are reported to reach levels of 0.2 μM after ingestion of 200 mg of tyramine in healthy individuals (Vandenberg et al. 2003). Reports of absorption of trace amines in vitro and in ex vivo systems suggests that trace amines in the gut may escape the degradative effects of monoamine oxidase enzymes, even in healthy epithelium.

Trace amine signaling has historically been studied in a wide spectrum of neuropsychiatric disorders, including attention-deficit hyperactive disorder, major depressive disorder, and schizophrenia. TAAR1 is strongly implicated in schizophrenia diagnoses and progression. Several studies have found that patients with schizophrenia have increased levels of tyramine or β-phenylethylamine in the urine (Potkin et al. 1979) and plasma (O'reilly et al. 1991; Shirkande et al. 1995), as well as an increase in comorbid inflammatory bowel disease or irritable bowel syndrome diagnoses (Gupta et al. 1997; Hemmings 2004). Perturbations to the microbiome are reported in both inflammatory bowel disease (e.g. Santoru et al. 2017) and schizophrenia (Severance et al. 2015, 2017), a phenomenon that is reversed with the successful administration of antipsychotics.

Attention-deficit hyperactive disorder (ADHD) is commonly associated with a dysregulation of the trace amine β-phenylethylamine (Baker et al. 1991). Extensive studies on the comorbidities of ADHD and gastrointestinal diagnoses are lacking, though current studies are suggestive that disruption to the gut-brain axis may plays a role in ADHD. Children diagnosed with ADHD exhibit changes to their microbiome compared to healthy controls, and administration of certain strains of bacteria within the first 6 months of life has been shown to have protective effects against ADHD (Felice and O'Mahony 2017). Additionally, preliminary studies indicate an increased level of pro-inflammatory cytokines and decreased levels of both tyramine and β-phenylethylamine in patients with ADHD (Baker et al. 1991; Sandgren and Brummer 2018), indicating a potential connection between the psychological condition and trace amine levels in the body.

Major depressive symptoms are also correlated with decreased urinary levels of β-phenylethylamine (Wolf and Mosnaim 1983), and therapeutics seeking to increase β-phenylethylamine levels naturally with exercise (Szabo et al. 2001) or replacement therapy with β-phenylethylamine (Sabelli and Javaid 1995) both appear to provide relief of major depressive disorder symptoms. Conversely, elevated urine β-phenylethylamine levels are correlated with manic disorders including bipolar affective disorder (Karoum et al. 1982; O'Reilly et al. 1991). Interestingly, there is a correlation of either a diagnosis of irritable bowel syndrome or inflammatory bowel disease within 1 year of diagnoses of depression (Kurina et al. 2001).

Discussion

The recognition of TAAR1 as a mediator for trace amines to act as chemical modulators of the brain-gut-microbiome axis opens up a new avenue for investigation on psychiatric and gastrointestinal disorder comorbidity as well as new

treatment avenues for these common disorders. The prevailing hypotheses in neuropsychiatric and gastrointestinal disorders suggest an interplay of genetic and environmental factors in the onset and propagation of disease. Trace amines and their primary receptor, TAAR1, have been widely studied for their involvement in the pathogenesis of neuropsychiatric disorders, which have high comorbidity with gastrointestinal disorders. With the emergence of greater understanding of the brain-gut-microbiome axis, it is now clear that both brain and gut share common communication molecules which can originate endogenously in the host or resident microbiome, or exogenously from ingested food. Here, we take the opportunity to review what is known about trace amines in the brain, the defined sources of trace amines in the gut, and our emerging understanding on the levels of trace amines in various gastrointestinal disorders. We summarize evidence that trace amines are ingested as well as produced by the microbiome, and that their receptor, TAAR1, is present in the gastrointestinal tract. Accordingly, novel TAAR1-targetted therapeutic compounds being advanced in clinical trials as new treatments for neuropsychiatric disorders could potentially have a therapeutic benefit through manipulation of the brain-gut-microbiome axis to modulate symptoms of neuropsychiatric disease. The localization of TAAR1 expression in the gut implicates a mechanism by which trace amines, as well as other endogenous or exogenous TAAR1 ligands, are implicated in inflammatory bowel diseases and the reported comorbidities of neuropsychiatric disorders and gastrointestinal disorders.

Although we focused on reviewing tyramine and β-phenylethylamine, it is important to acknowledge that there are additional trace amines, e.g. tryptamine, which are known in the human metabolome(Jeffery et al. 2012), which have similar effects to tyramine and β-phenylethylamine on gut motility and neurons (Williams et al. 2014), promoting adherence of bacteria to epithelial cells (Luqman et al. 2018), with identified accumulation in both colon cancer and irritable bowel syndrome (Ahmed et al. 2016; Bearcroft et al. 1998; Hong et al. 2011; Ponnusamy et al. 2011). It is also important to recognize that the levels of trace amines and the expression patterns of TAAR1 are highly dynamic and can be affected by diet, drugs, disease and psychological state. Likewise, the variable levels of trace amines may augment the secretion of neuromodulators into circulation, thereby modulating the levels of neurotransmitters in the brain (Yano et al. 2015). Both direct actions of trace amines on TAAR1 in the cells of the intestine and brain, as well as the secondary effects on neurotransmitters (e.g. serotonin, norepinephrine) remains to be further explored.

Localization in the intestine and luminal apical localization (Fig. 2) of epithelial cells in the gut and other polarized epithelia (thyroid) (Szumska et al. 2015) demonstrate a potential yet unexplored significance of TAAR1 in the gut. The commensal microbes of the microbiome niches on luminal apical membranes of the intestine. Additional studies are needed to understand if the effects of tyramine, β-phenylethylamine and other trace amines that are seen in in vitro epithelial cell lines are mediated by TAAR1. Similarly, TAAR1 may have an unappreciated role in the regulation of homeostasis in the gut, as TAAR1 may serve as a microbial sensor in the gastrointestinal tract mediating differentiation of the lumen or polarization of epithelial cells. To understand the role of the microbiota in the regulation of TAAR1 expression and activation, it would be prudent to study TAAR1 expression in germ-free mice or specific pathogen free mice, as some datasets in NCBI GeoData suggest a low level of TAAR1 expression in germ-free and specific pathogen free mice, though the conflicting detection of TAAR1 in RNA-seq data may be confounding these effects.

There is an underappreciated function and role of the so-called 'elusive trace amines' and their role in normal human physiology. The emergence of fecal metabolomic studies has classified trace amine levels at micromolar concentrations in the body for the first time, suggesting trace amines may be physiologically active in the gut (Jacobs et al. 2016; Santoru et al. 2017; Smith and Macfarlane 1997; Vandenberg et al. 2003; Kisuse et al. 2018). With the identification of TAAR1 expression in myriad cells in the intestine, there presents a great opportunity to further study complex mechanisms of the brain-gut-microbiome axis as it relates to intestine development, immune cell maturation as it relates to the 'hygiene hypothesis' for allergies and immunological disorders. Further, TAAR1 may serve as a novel therapeutic drug target to be further investigated for the treatment comorbid gut and neuropsychiatric disorders.

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