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Gut brain axis: diet microbiota interactions and implications for modulation of anxiety and depression

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The human gut microbiome is composed of an enormous number of microorganisms, generally regarded as commensal bacteria. Without this inherent microbial community, we would be unable to digest plant polysaccharides and would have trouble extracting lipids from our diet. Resident gut bacteria are an important contributor to healthy metabolism and there is significant evidence linking gut microbiota and metabolic disorders such as obesity and diabetes. In the past few years, neuroscience research has demonstrated the importance of microbiota in the development of brain systems that are vital to both stress reactivity and stress-related behaviours. Here we review recent literature that examines the impact of diet-induced changes in the microbiota on stress-related behaviours including anxiety and depression.

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Introduction

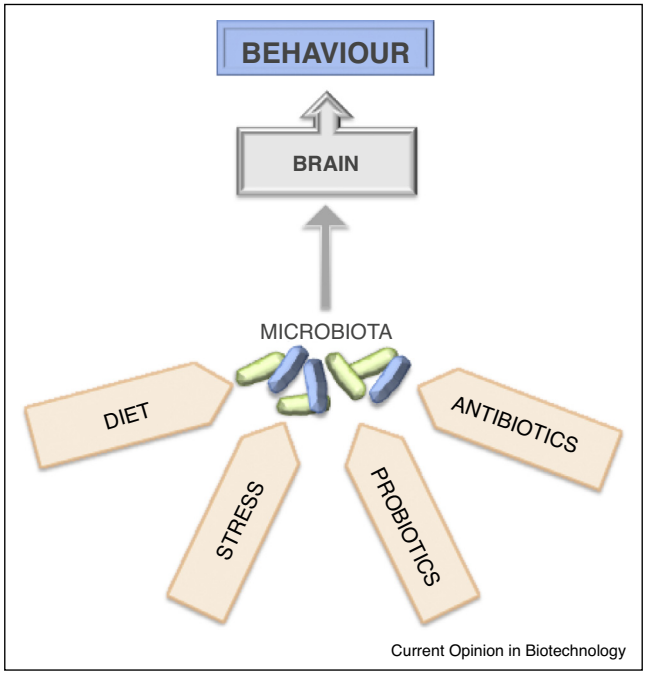
Diet and diet-related changes in gut microbiota influence the gut-brain axis and may in turn influence behaviours including anxiety and depression. A link between gut microbiota and anxiety-related behaviours has recently been established in mice [1–3]. Interestingly, a link between consumption of probiotic bacteria in fermented milk was also shown to influence brain activity in emotional centers in healthy individuals [4••]. This review will cover the latest literature related to microbiota and behaviour, diet-related mechanisms that may influence brain function and behaviour, and implications for modulation of anxiety and depression (Figure 1).

Gut microbiota and behaviour

In the past few years, a link between gut microbiota and stress-related behaviours has emerged in animal studies (see Table 1 for summary). The first experiments followed on the observation that germ free (GF) mice showed enhanced stress-reactivity [5] and sought to determine if this was associated with changes in anxiety-like behaviours. Surprisingly, the results revealed that GF mice showed reduced anxiety-like behaviour in the elevated plus maze (EPM), a well established behavioural test that examines approach and avoidance behaviour in mice, in comparison to specific pathogen free (SPF) mice. The low anxiety-like phenotype was accompanied by long-term changes in plasticity-related genes in the hippocampus and amygdala [6]. Interestingly, the low anxiety-like behavioural phenotype observed in GF mice persisted after colonization with SPF intestinal microbiota, demonstrating that gut–brain interactions influence CNS wiring early in life [2]. Following this initial report, two additional research groups reported reduced anxiety-like behaviour in GF mice using the EPM [3] and using the light dark test, a second approach/avoidance test used to test anxiety-like behaviour in mice [1]. A more recent paper using a different strain of mice (Balb/C compared to Swiss Webster and NMRI) showed that offspring of colonized GF mice (referred to as Ex-GF) had reduced anxiety-like behaviour in the open field test compared to GF mice [7]. In addition, these investigators showed the monoassociation with *Blautia coccoides* in GF mice reduced anxiety-like behaviour in open field, where as monoassociation with *Bifidobacterium infantis* reduced activity without effecting anxiety-like behaviour in the marble burying test [7] suggesting that the nature of the bacterial species employed influences the impact on behaviour. In GF stress sensitive rats (F344) increase anxiety-like behaviour was observed in a 6 min open field test compared to SPF rats that was associated with enhanced stress reactivity [8]. Both of the recent papers suggest that the interaction of gut bacteria and behaviour relies on strain of mice/rats and experimental design of the behavioural test.

Another important area of study is the relationship between stress, microbiota, and behaviour [9,10]. Using a mouse model of induced anxiety and depression via olfactory bulbectomy, investigators showed that elevated corticotropin-releasing hormone (CRH) expression, increased c-Fos activity, serotonin levels, and colon motility were associated with an altered intestinal microbiome [11], which was suggested to be due to the activation of

Figure 1



Factors influencing the gut–brain axis via microbiota. As reviewed in the article, diet, stress, probiotics, and antibiotics can impact gut microbiota community to influence microbiota to brain pathways and thereby impact behaviour.

the hypothalamic pituitary adrenal (HPA) axis [11]. In a different study that compared the effect of stress and/or antibiotics on the gut microbiome of mice, antibiotics were found to lower overall bacterial counts as expected, and with the addition of stress via the water avoidance stress test, a further reduction in the bacterial load was observed [12]. Analysis of the composition of luminal bacteria using fluorescence *in situ* hybridization revealed that stress alone resulted in a loss of Verrucobacteria, a twofold increase in *Clostridium* spp., and the added presence of a low abundance population of *Lactobacillus/Enterococcus* spp. Antibiotics alone similarly reduced Verrucobacteria but also reduced *Clostridium* spp. and significantly increased Enterobacteria and the *Lactobacillus/Enterococcus* spp. population. The combination of stress and antibiotics created yet another novel environment with a sixfold reduction in *Clostridium* spp. and significant increases in Verrucobacteria, Enterobacteria, and *Lactobacillus/Enterococcus* spp. [12]. The study highlights the dynamic nature of how host–microbiota interactions and stress may modulate microbiome profiles [12]. In a related report from the same research group, changes in the expression of gut sensory markers were shown to be associated with changes in *Bacteroides* spp., *Lactobacillus* spp., and *Bifidobacterium* spp., however changes in gut microbiota composition did not alter expression of toll-like receptors [13]. A similar stress and antibiotic study in rats also identified a decrease in overall bacterial diversity in distal ileum of the chronic stress group compared to the control group, with no accompanying difference in the overall bacterial load, and this dysbiosis was characterized by the reduction of less-abundant members of the bacterial community [14]. The addition of rifaximin treatment in stressed rats significantly decreased the total bacterial load, altered the microbial community leading to a dominance of Lactobacilli, and prevented the increase of gut permeability induced by the stress trials, a finding that suggests the antibiotic protects intestinal barrier function by modulation of the gut microbiome [14].

In a clinical study focused on further exploration of the link between microbiota composition and depression, researchers observed a general underrepresentation of the Bacteroidetes phylum in depressed patients and an association of the Lachnospiraceae family with the depression group, and interestingly, even with a decrease in Bacteroidetes, specific operational taxonomic units (OTUs) identified as members of the Bacteroidetes phylum correlated with depression [15]. It has been suggested that increased gut permeability and related bacteria translocation may contribute to increased inflammation in depressed individuals [16]. Recently, evidence supporting this suggestion was provided by a clinical study that observed elevated serum levels of IgM and IgA against the lipopolysaccharide (LPS) of gut commensals in patients with depression [17].

Potential mechanisms underlying microbiota-related changes in behaviour

A number of dietary factors have been shown to have an impact on behaviour including anxiety-like and depressive-like behaviours. For example, long-term feeding of a high fat diet increases anxiety-like and depressive-like behaviour in mice and rats [18–20]. Interestingly GF mice, lacking microbiota, are smaller than age-matched SPF mice and have reduced anxiety-like behaviour that may be linked to metabolic changes due to the absence of microbiota. Central changes in brain expression of feeding peptides have been reported in GF mice compared to conventionalized mice [21]. GF mice show reduced body weight and epipidymal fat weight, in spite of increased food intake [22] revealing the requirement of microbiota for fat storage. Evidence supports a role for elevated levels of fasting-induced adipose factor (Fiaf), a lipoprotein lipase inhibitor, in this phenotype [22,23]. In conventionally raised mice, low levels of Fiaf are produced by gut epithelium over development, whereas in GF mice, Fiaf expression is upregulated during the transition to weaning (3–4 postnatal week) and circulating levels remain high into adulthood [22]. In adulthood, the peripheral metabolic phenotype of GF mice includes reduced plasma levels of leptin, insulin, and glucose [22,24]. Remarkably, GF mice are resistant to high fat