

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Gut-Brain Axis: Probiotic, *Bacillus subtilis*, Prevents Aggression via the Modification of the Central Serotonergic System

Heng-Wei Cheng, Sha Jiang and Jiaying Hu

Abstract

Intestinal bacteria release various neuroactive compounds directly or indirectly regulating brain function to modulate host health and behavior through the gut-brain axis. Probiotics have been used as dietary supplements to target gut microbiota (microbiome) for prevention or therapeutic treatment of various diseases including mental disorders. In our study, chickens were used as an animal model to assess, if dietary supplementation of probiotic, *Bacillus subtilis*, reduces aggressive behaviors following social challenge. Chickens of an aggressive line were housed in single-hen cages. At 24 weeks of age, the hens were paired with similar body weight to identify the dominance rank (day 0). The subordinate and dominant of each pair were fed a regular layer diet or the diet mixed with 250 ppm probiotics for 2 weeks, then the second behavior test was performed between the same pair (day 14). The display of aggressive behaviors in the regular diet-fed chickens was not affected between the levels at day 0 and day 14, while the frequency of threat and aggressive pecking were reduced in the probiotic-fed chickens compared to the levels at day 0. These results suggest dietary probiotic, *Bacillus subtilis*, could be a suitable strategy for increasing hosts' mental health.

Keywords: probiotics, *Bacillus subtilis*, aggression, serotonergic system, gut-brain axis

1. Introduction

Human emotional susceptibility in an inter-group is associated with individual differences in the functions of the hormonal and/or neurochemical systems in response to internal and external stimulations. Aggression, as one of emotional disorders, has been commonly defined as feeling of anger or antipathy of an organism during social interaction, leading to hostile or violent behavior or attitude, provoking attack or confront toward another individual [1]. Aggression affects millions of people's health and welfare around the world annually, resulting in significant social destruction and economic costs.

Intestinal bacteria, as a virtual endocrine organ, release various neuroactive compounds directly or indirectly regulating brain function, including the serotonergic system, to regulate host health and behavior through the gut-brain

axis [2–10]. Intestinal bacteria, as well as *Bacillus subtilis*, used as probiotics are involved in tryptophan metabolism [11–14]. Tryptophan metabolites have roles in protecting intestinal mucosa from inflammation and regulating gut immune homeostasis [15–18]. Tryptophan, a precursor of 5-HT, directly affects brain 5-HT synthesis as that tryptophan can pass the brain-blood barrier [19, 20]. The brain serotonergic system plays a critical role in regulating behaviors, especially aggression [21, 22]. Concentrations of 5-HT and its metabolites, as well as the density of 5-HT receptors, have been used as major indicators of aggressive behaviors in humans and experimental animals [23–26].

Probiotics (also called psychobiotics or bio-friendly agents), defined “as a source of live (viable) naturally occurring microorganisms (direct-fed microbials, DFMs)”, have been used as dietary supplements to target gut microbiota (microbiome) for a novel promising therapeutic approach of various diseases including social stress-induced mental disorders in humans and various experimental animals [27–36]. Different probiotic strains, for example, have been investigated as functional food or therapeutic treatment of various diseases, including *Bifidobacterium bifidum* [37–39]; *Bifidobacterium bifidum* (BGN4) and *Bifidobacterium longum* (BORI) [40, 41]; *Bifidobacterium pseudocatenulatum* [42]; *Lactobacillus helveticus* [31, 32]; *Lactobacillus plantarum* [43]; *Lactobacillus paracasei* (KW3110, [44]); *Lactobacillus rhamnosus* [45]; and *Clostridium butyricum* [46]. The results collected from these studies indicate that the effects of probiotics on physiological homeostasis, immunity, stress resistance, and related health status are affected by multiple factors, including the probiotic species, its concentration, and duration as well as the host’s age and health status [47, 48].

Bacillus subtilis, as one of the three most common species of probiotic products in the United States [49], has been widely used as functional feed supplements, such as in a number of dairy and non-dairy fermented foods, for improving human health and well-being [50–52]. Similarly, *Bacillus subtilis*, as growth promoters, has been demonstrated to improve chickens’ growth performance [53–55]; regulate intestinal microstructure [56] and digestive enzymes [57, 58]; synthesize and release antimicrobial and antibiotic compounds [15, 59–63]; increase immunity [57, 64] and neurochemical activities including serotonin [8, 65, 66] as well as affect animal behavior [67, 68] following various stressors. In addition, *Bacillus subtilis* can overproduce L-tryptophan [11, 69], consequently increase 5-HT in the hypothalamus [70], function as an antidepressant and anti-anxiety agent [71, 72], and eliminate nervous tension in mice [73]. In the current study, chickens were used as an animal model to assess if dietary supplementation of probiotic, *Bacillus subtilis*, reduces aggressive behaviors following social challenge.

2. Gut microbiota and the gut-brain axis

Gut microbiota is a collective name of ten of trillions of microorganisms living in our intestine, including more than 35,000 different species of known bacteria [74]. Microbiome refers to the collective genomes of more than 3 million genes of the microorganisms in a particular environment. Gut microbiota, like a virtual endocrine organ, reacts to various internal and external stimuli [5, 75–78]. Consequently, gut microbiota influences and regulates hosts’ health and mood status including aggression by integrating metabolic, immune, endocrine, and neural reactions through the bidirectional communication of the gut-brain axis (**Figure 1**) [7, 33, 79–83]. Gut microbiota in hosts, for example, regulates brain neurotransmitters [84–87] such as serotonin (5-HT) through releasing its precursor, tryptophan, an essential amino acid [75, 88–90]. Serotonin is a key neurotransmitter within the brain, contributing to the development of the central nervous system (CNS)

[91–94] and social behavior [95, 96], affecting mental health [97–100] and providing therapeutic strategy for treating or preventing stress reaction and related neuropsychiatric disorders [94, 97].

2.1 Social stress and the hypothalamic-pituitary-adrenal axis

The social world is filled with different types of interactions, such that social challenges (fight-or-flight) and social environmental changes (group instability), as stressors, can cause highly potent stress [101–103]. Some management practices used in the intensive farm animal production systems, for example, may cause stress in animals. Farm animals are often housed in large groups at high densities, and during the animals’ lifetimes, they are repeatedly transported to new environments and mixed with unfamiliar individuals. Based on the social network theory, animal group disruption can lead to social stress and related aggression [104] when they are unable to cope with these management practices and/or to reset their dominance rank (a form of animal social structure hierarchy) [105, 106].

Aggression has been commonly defined as feeling of anger or antipathy during social interactions, leading to hostile or destructive behaviors or attitudes, provoking physical or verbal attack or confront toward another individual [1]. Aggressive encounters among conspecifics for obtaining or maintaining a socially dominant position or rank cause a negative or unstable social environment to activate the hypothalamic-pituitary-adrenal (HPA) axis which is known as the key stress response system [107–109]. Cortisol (or corticosterone, CORT, in rodents and birds), as one of the final hormones released from the adrenal cortex, has multi-functional functions in both normal and abnormal states, regulating behavioral styles, metabolic patterns, and endocrine and immune functions, and ensuring an adequate coping strategy and well-being [110–112]. In mammals, hypercortisolism in response to novel environment exposures has been evidenced to be of adrenal origin [113, 114]. The value of circulating cortisol (or CORT) has been used as a criterion of stress response in humans and various animals [115–117]. Corticotrophin-releasing factor facilitates aggression [118, 119], and related elevation of CORT (or cortisol) also affects neuroendocrine functions through binding to their receptors [120, 121], causing neuron loss in the hippocampus [122], dysfunction of the serotonergic system [123], and inhibition of immunity (increased pro-inflammatory cytokines as neuroinflammatory response) within stress-sensitive brain regions [124]. These changes finally lead to the development of psychological disorders such as aggression [109, 125]. Similar to that the HPA hyperactivity generates aggressive behavior, exogenous glucocorticoid treatments increase exacerbated aggressiveness in both humans and experimental animals [123, 126]. Taken together, emerging

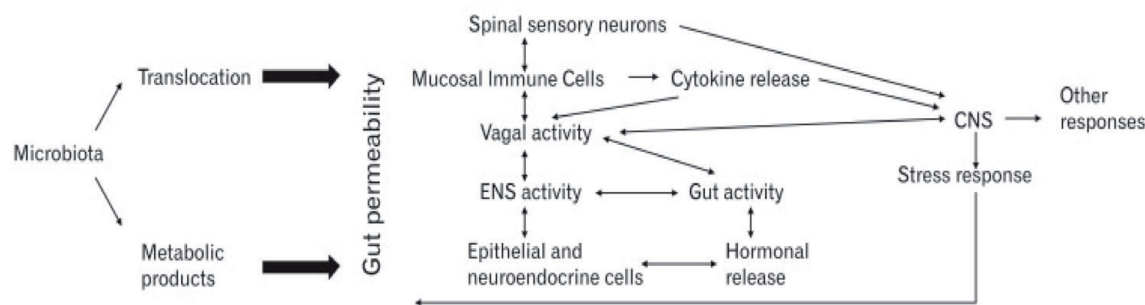


Figure 1. The microbiota-host interaction occurs at the level of the gastrointestinal mucosa via local neural, endocrine, and immune activities, influencing brain neurotransmitter expression, physiological homeostasis, and immunity (modified from [79]).

evidence have indicated that the changes of the programming of HPA stress reactivity [127] cause long-term effects on the host physiological homeostasis and neurobehavioral functions [128].

2.2 Microbiota, stress-associated aggression

Aggression within a group is to establish a dominance hierarchy when the animals are first brought together in a common environment [129–131]. From an evolutionary perspective, aggression is adaptive behaviors that are related to an individual's survival, growth, and reproductive success within a group [132, 133]. However, aggression with long-term impact is often destructive and maladaptive in today's society, affecting millions of people's health and well-being around the world annually, resulting in significant social destruction and economic costs [134–136].

Intestinal microbiota plays an important role in regulation of social behavior, emotional expression, and mental health within the animal kingdom [3, 137, 138]. They are essential players in stabilizing homeostasis of the GI tract in response to both acute and chronic stress via the microbiota-gut-brain axis [16, 139]. Normally, intestinal microbiota provides protection for animals by competing for attachment sites and nutrients with pathogens as well as production of antimicrobial peptides and neuroactive compounds [140, 141]. The gut microbiota is also a key pathway to modulate brain processing the integrated information received from the peripheral nerve systems (the vagus nerve, enteric nerve, and autonomic nervous system), hormone signaling, the immune system, and microbial metabolites (short-chain fatty acids) [5, 137]. Under social challenges, stress and related oxidative damage cause anatomical and functional disorders of the GI tract by: (1) disrupting the commensal bacterial populations and colonization, thus reducing beneficial bacteria and increasing pathogens; (2) increasing pathogen survivability and innovating capability; (3) disrupting absorption of nutrients and minerals, including calcium; (4) disrupting microbial neuroendocrine functions; (5) disrupting the gut epithelial barrier, thereby increasing intestinal permeability causing the gut to leak certain bacteria (leaky gut), resulting in metabolic disorder; (6) damaging epithelial cells, thus producing free radicals and reducing antioxidant efficacy; and (7) interrupting intestinal integrity, thereby leading to intestinal inflammation [142–144]. These changes in gut microenvironment affect brain functions, resulting in exacerbated HPA axis activity, increased chronic inflammation, and/or disrupted neurotransmitter balance, leading to emotional damage [139, 145] and mental disorders [137, 138]. Sudo et al. [146] reported a correlation between the changes of gut microbiota and the function of the HPA axis. Germ-free (GF, antibiotic-treated microbiota-deficient or raised without any exposure to microorganisms) rats show exaggerated HPA responses to psychological stress [75, 147] with significantly higher levels of both ACTH and CORT in response to restraint stress compared to control rats [146]. In GF mice, gut microbiota also modulates the 5-HT synthesis and release at both the brain and peripheral levels directly and indirectly via the microbiota-host interactions [148]. Reduced 5-HT activity (a 5-HT deficiency) has been associated with personality traits (interspecific social behavior), such as impulsivity and aggression, and deteriorated stress coping capability (increased stress response) in humans and various animals [149, 150] including chickens [24, 151–154].

3. Serotonin and aggression

Serotonin, as an ancient chemical, is a key neurotransmitter. It plays a critical role in shaping social responses by regulating both basic (proactive) behaviors

(such as feeding, drinking, and sexuality) and reactive behaviors (fearfulness, anxiety, and cognition) including aggressive behaviors [155, 156] and mood disorders [157, 158]. Abnormalities of blood and brain levels of 5-HT, 5-HIAA (its metabolite, 5-hydroxyindoleacetic acid), tryptophan, and its receptors have been used as major indicators or targets in the diagnoses and treatments of psychiatric and compulsive disorders in humans and various experimental animals [62, 63, 159, 160].

In the CNS, 5-HT functions to inhibit aggression, thereby controlling domestic behaviors [161–163]. The 5-HT deficiency theory of aggression is driven from the negative correlation between the changes of the CNS 5-HT and aggressiveness in humans [164, 165], non-human primates [166], rodents [25, 167], and chickens [24, 168]. Aggressive animals have low levels of 5-HT in the brain, including in the hypothalamus [169–171]. Experimental increase of 5-HT and/or 5-HIAA in the brain, such as in the lateral hypothalamus and amygdala, blocks or retracts killing behavior in rodents [172, 173]. Hypothalamic injection of a 5-HT_{1a} agonist inhibits aggression in male hamsters [174]. Depletion of brain 5-HT in TPH2 mutant mice marks aggression and lowers habituation in novel environments [149]. In addition, 5-HT_{1BR} knockout mice show increased aggression and impulsivity [175, 176]. The implication of 5-HT successfully relieves the depression syndromes in humans [177] and reduces aggressive behaviors in primates and rodents [178, 179].

In the peripheral system, however, pathophysiological roles of 5-HT in behavioral and motivational regulations are unclear. Reduced, elevated, and unchanged blood 5-HT concentrations have all been reported in association with behavioral dysfunctions, including aggressiveness [180, 181]. The conflicting data from different investigations could be related to the differences in species of animals, behavioral evaluations, and/or stressors used as well as duration and frequency of stressors presented.

4. Chicken as an animal model for social stress and related aggression

Human emotional susceptibility in an inter-group is associated with individual differences in the functions of the hormonal and neurochemical systems in response to internal and external stimulations [182, 183]. Various social and biological factors are associated with the development and expression of aggressive behaviors, including environmental, genetic, cognitive, hormonal, and neurotransmitter circumstances [184]. Aggression and associated mental illness are an emerging public health problem [29]. Animal models are critical for investigating the potential biological processes involved in human aggression and mental disorders.

Although there are dissimilarities between humans and chickens, as indicated, the neural circuitry for aggression and social behavior appear to be evolutionarily conserved across the vertebrates [185]; chickens have been used as an animal model in various clinical and psychopharmacological studies, such as anxiety, depression, and aggression [186, 187]. A commercial hen can have more than 300 offspring with similar genetic characteristics during her lifetime, and chicks can be hatched without maternal condition effects. Previous studies have reported that birds' brain possess a core "social behavioral network" which is homologous to the social behavioral network of mammals [188]. There are evidences that the central nuclei involved in moodiness in avian, at least in part, are morphofunctional homologous to the mammalian nuclei [189], such as the hypothalamus [190], nucleus taeniae (homolog to the amygdala of mammals, [191, 192]), and Raphe nucleus [193]. These nuclei exert similar cognitive abilities and consciousness [194] with capability of plasticity in response to environmental stimulations [195]. In addition, there are similar distributions of neurotransmitter receptors, including serotonergic receptors

Behavior	Description
Feather pecking	One bird pecking at feathers of another bird, can be gentle (nibbling or gentle pecking in which feathers are not removed or pulled) or severe (vigorous pecking to feathers in which feathers are often pulled, broken, or removed)
Threat	One bird standing with its neck erect and hackle feathers raised in front of another bird
Aggressive pecking	Forceful downward pecks directed at the head or neck of other birds
Threat kick	One bird forcefully extending one or both legs such that the foot strikes another bird

Table 1.
Behavioral ethogram.

between birds and mammals [196, 197]. Particularly, it has been evidenced that the development and function of avian HPA axis in response to stimuli are analogous to those of mammals [198, 199] and there are similar distributions of cortisol-like molecules in the same organs from both birds and mammals [200]. Birds' CORT biosynthesis and metabolism can be stimulated in the same way as that of mammals [201–203]. During breeding, functional integrations among behavior, physiology, morphology, and environment in chickens may create suites of various traits that are simultaneously acted upon each selection program [204]. For example, selection based on individual production capability (phenotypic characteristics) increases animals' competition and aggression [205, 206] such as potentially injurious feather pecking and cannibalism. For instance, through more than 20 years of selection, egg production had been increased significantly in a former commercial Dekalb XL strain, whereas mortality due to aggression and cannibalism in non-beak trimmed hens had also increased about 10-fold [132, 152].

Results from previous studies conducted in our laboratory have found that chicken strain differs in social reactions through a diversely genetic selection program. The DXL hens have distinct stress levels in attempting to adapt to their social environments [207, 208] and exhibit different levels of aggressiveness [168]. In addition, neurotransmitters, 5-HT and dopamine (DA), and the hypothalamic-pituitary-adrenal (HPA) axis are regulated differently between chicken strains [168, 207]. There results suggest that injurious behaviors and related social sensitivity of chickens, similar to that in mammals, are regulated via the serotonergic system and the HPA axis [123, 209], and mechanisms underlying aggression in laying hens may be analogous to those of humans and rodents [210]. Similarly in humans and rodents, stress-induced destruction of intestinal bacteria disturbs the bilateral connection of the microbiota-gut-brain axis in chickens, affecting physiological homeostasis and behavioral exhibition [211]. In one of our studies, the role of probiotic, *Bacillus subtilis*, on aggression in DXL line was examined. In the study, one-day-old female chicks were reared in single-bird cages up to 24 weeks. At 24 weeks of age, the hens with similar body weight were paired for the first aggression test (pre-treatment, day 0) in a novel floor pen [212]. Behaviors were video-taped for 2 h immediately after releasing the two hens simultaneously into the floor pen to determine the dominant individual per pair. Following the behavioral test, the subordinate hens were continuously fed the regular diet, while the dominant hens were fed the diet mixed with 250 ppm probiotic (1.0×10^6 cfu/g of feed) for 2 weeks. The probiotic contains three proprietary strains of *B. subtilis*. After the treatment (day 14), the second aggression test was conducted within the same pair of hens. The video recording was analyzed for frequency of feather pecking, threat, aggressive pecking, and threat kick by the routine lab procedures (Table 1) [154, 213].

5. Probiotic, *Bacillus subtilis*, and aggression

As social animals, chickens show fear, depression, and/or anxiety in novel environments and show aggression toward ones for establishing social dominance rank in unfamiliar social groups [214, 215], which is similar to rodents used in human psychopharmacological studies [216, 217]. The paired social ranking-associated behavioral test used in this study has been routinely performed in chicken behavioral analysis [154, 213, 218]. The rationale and cellular mechanisms of the test is similar to the resident-intruder test which is a standardized method used in rodents for detecting social stress-induced aggression and violence [219, 220].

5.1 Probiotics and *Bacillus* spp.

A healthy intestinal microbiota community is important for maintaining physiological and behavioral homeostasis as that the gut microbiota regulates appetite, local and systemic immunity, stress responses of the HPA and sympathetic-medullary-adrenal (SMA) axes, and circadian rhythms [5, 221]. The new strategies of psychotherapy aimed at restoring the normal gut microbiota and intestinal homeostasis have been developed for the prevention and/or reduction of stress-induced abnormal behaviors and mental disorders.

Probiotics are commensal bacteria ("direct-fed microbials", DFM) that offer potential health beneficial bio-physiological effects to the host's stress response (acute, chronic, or both). Probiotics aid animals in adapting to their environments and protect against pathogens by: (1) altering the microbiota profile with beneficial bacteria to prevent the growth of pathogens and to compete with enteric pathogens for the limited availability of nutrient and attachment sites; (2) producing bacteriocins (such as bacteriostatic and bactericidal substances) and short-chain fatty acids against pathogens to regulate the activity of intestinal digestive enzymes and energy homeostasis and to increase mineral solubility; (3) reducing oxidative stress, inflammation, and acinar cell injury; (4) modulating host immune and inflammatory responses and restoring the intestinal barrier integrity which prevents pathogens from crossing the mucosal epithelium; (5) stimulating the endocrine system and attenuating stress-induced disorders of the HPA and/or SMA axes via the gut-brain axis; and (6) inducing epithelial heat shock proteins to protect cells from oxidative damage; and (7) synthesis and secretion of neurotransmitter such as 5-HT and tryptophan [16, 17, 222–226]. In both human and rodent studies, probiotics reduce cognitive dysfunction, decrease the stress response and related oxidative damage by lowering plasma CORT and ACTH levels, restore hippocampal 5-HT levels, and normalize immunity with low plasma levels of TNF- α (tumor necrosis factor- α), a proinflammatory cytokine, but high levels of IL-10 (Interleukin-10), an anti-inflammatory cytokine [67, 227–230]. It has been stated in nonhuman primate models that the composition of the gut microbiota has potential effects on hosts' aggressive behaviors and anxiety symptoms [127], which is similar to the findings reported in humans [137, 231–233]. In rodent studies, GF animals with exaggerated HPA responses to social stress can be normalized by certain probiotics [147]. In addition, probiotics have successfully attenuated anxiety and depressive behaviors in rat offspring separated from their mother [234–236] and the obsessive-compulsive-like behaviors in house mice [28, 237]. These results support the psychobiotics theory [238] and provide a new insight into the possible use of probiotics to improve a host's cognitive function in humans [9, 40, 41, 239–243].

A proposed strategy for improving human health is dietary supplement with probiotic microorganisms including *Bacillus* species [52, 244]. *Bacillus subtilis* is spore-forming bacteria. They have heat stability and low pH-resistance (the

gastric barrier), and tolerate multiple environmental stressors [245, 246]. Several *Bacillus* spp. such as *B. coagulans* and *B. subtilis* have been used as probiotics in both humans [247–249] and animals [246] including poultry [65, 67, 250, 251]. Several mechanisms of action of *Bacillus* spp. have been proposed: the improvement of hosts' growth, survival, and health status via their anti-inflammatory functions through immunomodulation and cytoprotection [252, 253]. And, they have been used as antibiotic growth promoters alternatives with health-promoting benefits by naturally synthesizing proteins, enzymes, antimicrobial peptides, vitamins, gut flora modulation to promote beneficial microbiota along the GI tract and to correct and repair immunological and gut morphological alterations [244, 246, 250, 254, 255]. In addition, numerous studies have shown that probiotic-induced changes in the composition of gut microbiota lead to alterations of neuroendocrine functions. For example, in response stimulations, *B. subtilis* alleviate oxidative stress, provoke a specific biological response, and improve mood status of hosts via the gut-brain axis [52, 147, 256].

5.2 *Bacillus subtilis*-based probiotic and social challenge-induced aggression

Aggression, in nature, is associated with competition (natural selection) for survival and reproduction [22, 257, 258] (please also see above for the detailed description). However, in artificial production environments, such as in the poultry industry, aggression causes increased social stress and feather and body damage, in some instances these injuries leading ultimately to cannibalism. Cannibalism is a major concern related to non-beak trimmed bird deaths in current housing environments [259, 260]. Beak trimming (BT) is a routine procedure practiced in the US egg industry for reducing social stress by preventing and/or inhibiting feather pecking and cannibalism. However, BT is criticized for causing tissue damage and pain (acute, chronic, or both), negatively affecting the welfare of billions of chickens annually [261, 262]. Considerable concern from the public has led to a growing movement against procedures causing pain and suffering in farm animals. In response to growing pressures, housing environments of laying hens have been modified and/or various dietary supplementations have been provided in attempts to prevent social stress and stress-associated injurious behaviors. For instance, modifications include reducing light intensity, changing the nutritive value or taste of diets [263–265], providing straw or grain [266, 267] or pelleted diets [263], housing hens in floor-pens [268], and developing enriched cages [269, 270]. However, these methods have had limited success and provide no guarantee of preventing these injurious behaviors. Therefore, an obvious solution is to develop a welfare-friendly alternative to BT that minimizes social stress, thereby preventing feather pecking and cannibalism. The hypothesis was tested in this study: probiotics could be an alternative to beak trimming in chickens for reducing feather pecking and aggression via regulating the gut-brain axis.

Based on the 5-HT deficiency theory of aggression, social challenge-induced changes in 5-HT concentration were examined in this study. In the current study, the data showed that prior to the treatment (day 0), plasma 5-HT levels were higher (26% increase) in the dominant hens than that of subordinate hens but were not statistically significant ($P = 0.24$. Dominant_{5-HT} = 17.46 ng/ml, Subordinate_{5-HT} = 13.87 ng/ml). This finding is in agreement with the results reported previously [152, 168]. In those studies, higher plasma levels of 5-HT were detected in hens from mean bad bird (MBB) strain, a high aggressive strain selected for both low productivity and low longevity resulting from injurious pecking and cannibalism, compared to hens from kind gentle bird (KGB), a low aggressive strain selected for both high productivity and high longevity. In

addition, Bolhuis et al. [271] proposed that blood 5-HT activity is correlated with the development of severe feather pecking in laying hens. A similar correlation between blood 5-HT levels and aggressiveness has also been detected in humans and various other animals, that is, a lower blood 5-HT level was associated with less aggressive individuals in humans [180, 272] and canine [273], while an elevated blood 5-HT level was determined in patients with aggressive behaviors [274] and in aggressive teleost fish [275].

Post-treatment (day 14), plasma 5-HT levels were reduced toward the levels of controls (subordinates) in the probiotic fed dominant hens ($P = 0.02$) compared to their related levels prior to treatment (day 0) (**Figure 2**). There were no treatment effects on plasma 5-HT concentrations in subordinate hens fed a regular diet ($P = 0.88$). Although the reasons of the reduction of plasma 5-HT concentrations in probiotic fed hens are still unclear but could be similar to those proposed in probiotic-treated patients with intestinal inflammatory disorders such as irritable bowel syndrome (IBS) and IBS experimental animals. Probiotics reduce IBS-associated abdominal pain and abnormal bowel habits [276, 277] through regulation of both the central and peripheral serotonergic systems via the microbiota-gut-brain axis [278, 279] and gut epithelial enterochromaffin cells [19]. In the peripheral system, probiotics reduce or inhibit IBS-associated serotonergic system abnormalities, that is, great hypersensitivity and spontaneous release of 5-HT [280, 281]. Serotonin reuptake transporter (SERT or 5-HTT) has functions in inactivating 5-HT. Down-regulation of SERT receptors has been found in the intestinal mucosa of IBS patient whose symptoms are similar to those found in the SERT knockout mice [282]. Serotonin 5-HT₃ receptor antagonist also has shown efficacy in treating IBS patients [278, 283]. In addition, Wikoff et al. [284] reported that conventional mice had lower concentrations of 5-HT compared to GF mice. GF mice also had an exaggerated stress response [146] with anxiety-like behaviors [285]. These abnormal behaviors in GF mice can be inhibited or reduced by feeding probiotics [286] or transplanting fecal samples of conventional mice [287]. The current and previous

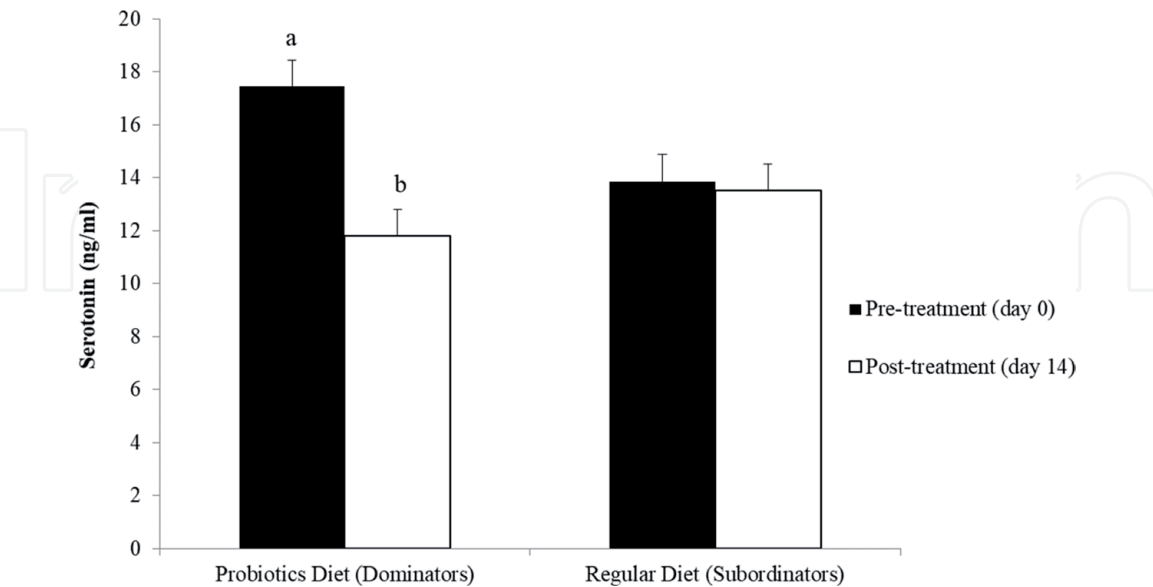


Figure 2. Plasma serotonin (5-HT) levels at day 0 (pre-treatment) and day 14 (post-treatment) in probiotic fed dominant hens and regular diet fed subordinate hens. Compared to subordinate hens, plasma 5-HT concentrations were higher in dominant hens at day 0 but without statistical difference ($P = 0.24$); the difference disappeared at day 14. Compared to the levels at day 0, blood concentrations of 5-HT were reduced in probiotic fed dominant hens at day 14 ($P = 0.02$) but were not in regular diet fed subordinate hens ($P > 0.05$). ^{a,b} between the concentrations at day 0 and day 14, least square means lacking common superscripts differ ($P < 0.05$).

results indicate that normal health gut microbiota plays an important role in regulating social stress and stress-associated behaviors.

Whether the changes of blood 5-HT levels in probiotic fed dominant hens represent a similar change of 5-HT concentrations in the brain is unclear, as 5-HT cannot pass the brain-blood barrier and is regulated differently between brain neurons and peripheral tissues [288]. The plasma 5-HT is synthesized mainly by the EC cells of the gut and stored in the platelets [289]. However, it has been proposed that platelet 5-HT uptake is a peripheral marker of brain 5-HT [273]. Dietary probiotic, *Lactobacillus plantarum* strain PS128, increases the levels of 5-HT as well as dopamine in the striatum, which is correlated with the improvement of anxiety-like behaviors in GF mice [290]. Similar results have been received from our current studies. In one study, chickens (broilers) were fed *Bacillus subtilis* from day one. At day 43, *Bacillus subtilis* fed chickens had higher levels of 5-HT in the raphe nuclei and lower levels of norepinephrine and DA in the hypothalamus than controls [291]. Probiotic fed chickens also had improved bone traits (bone mineral density, bone mineral content, and robusticity index). Under heat stress (32°C), *Bacillus subtilis* fed chickens had lower heat stress-related behaviors and inflammatory response and reduced IL-6 levels in the hypothalamus compared to controls [67]. Further studies, however, are needed to examine if there are correlations between the regulations of peripheral 5-HT and CNS 5-HT in probiotic fed hens.

The gut commensal microflora may have an indirect effect on 5-HT synthesis by regulating tryptophan metabolism. The degradation of tryptophan, a precursor of 5-HT, is mainly through the kynurenine pathway which regulates over 95% of tryptophan in the peripheral system and is functionally mediated by gut microbiota and probiotics [147, 292]. In the present study, the tryptophan level was not significantly affected by dietary probiotic ($P = 0.35$), but the initial levels of tryptophan in dominant hens were approximately 28% higher than the subordinate hens ($P = 0.21$) (**Figure 3**). The pattern of changes in blood concentrations of tryptophan in probiotic fed dominant hens was correlated with the changes of peripheral concentrations of 5-HT, indicating that probiotic may directly or indirectly regulate 5-HT synthesis in the peripheral system.

In this study, behavioral changes in dominant hens were correlated with the changes of blood 5-HT concentrations following fed probiotic. In the probiotic fed dominant hens, the levels of threat kick were reduced (**Figure 4a**, $P = 0.04$), and the frequency of aggressive pecking tended to be lower (**Figure 4b**, $P = 0.053$). The levels of feather pecking in dominant hens were reduced compared to their initial levels at day 0 but without statistic significant (**Figure 4c**, 58%, $P > 0.05$). There was no change in injurious behaviors in the regular diet fed subordinate hens between day 0 and day 14 (**Figure 4a–d**). The same or similar cellular mechanisms proposed in humans and rodents may be applied to the changes in the probiotic fed dominant hens. In humans and rodents, probiotics directly manipulate commensal bacteria releasing neuroactive factors, such as 5-HT and norepinephrine [8], and indirectly affect the neurotransmitter metabolisms, such as tryptophan as well as cytokines, through the microbiota-gut-brain axis [5, 40, 41, 279, 293–297]. In addition, the effects of probiotics, including *B. subtilis*, on behavioral exhibitions have been conducted on GF mice. Bercik et al. [287] reported that anxiety behaviors can be induced in less anxious phenotypic mice by colonization of the gut bacteria from anxiety-like phenotypic mice (FMT, fecal microbiota transplant). Probiotics also have therapeutic effects on neurodevelopmental disorders [28, 95, 298–301], for example, reduced anxiety-like behaviors by providing *L. helveticus*, *Mycobacterium vaccae*, and/or *Bifidobacterium* strains [231, 287, 302, 303], and alleviated autism-related stereotypic behaviors by treating with *Bacteroides fragilis* [304] and behavioral dysfunction with *Lactobacillus reuteri* [301, 305].

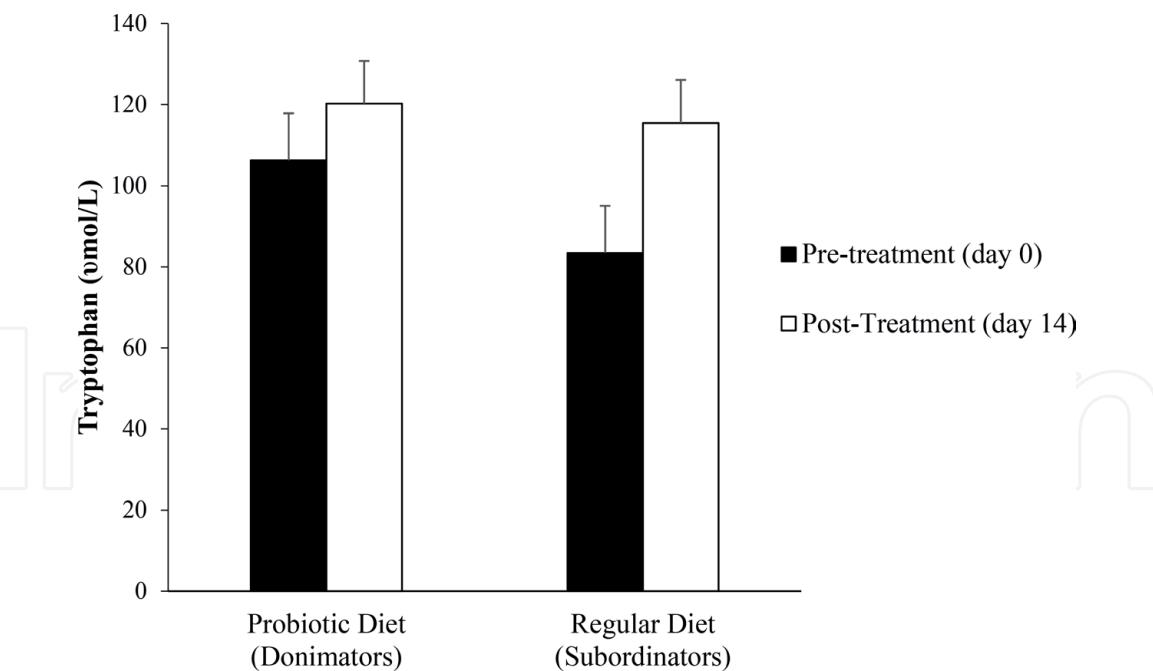


Figure 3. Plasma tryptophan levels at day 0 (pre-treatment) and day 14 (post-treatment) in probiotic fed hens and regular diet fed hens. Prior to treatment, dominant hens had higher tryptophan concentrations compared to subordinates but the difference did not reach statistical difference ($P = 0.21$). There were no treatment effects on tryptophan concentrations in both probiotic fed hens and regular diet fed hens ($P > 0.05$, respectively).

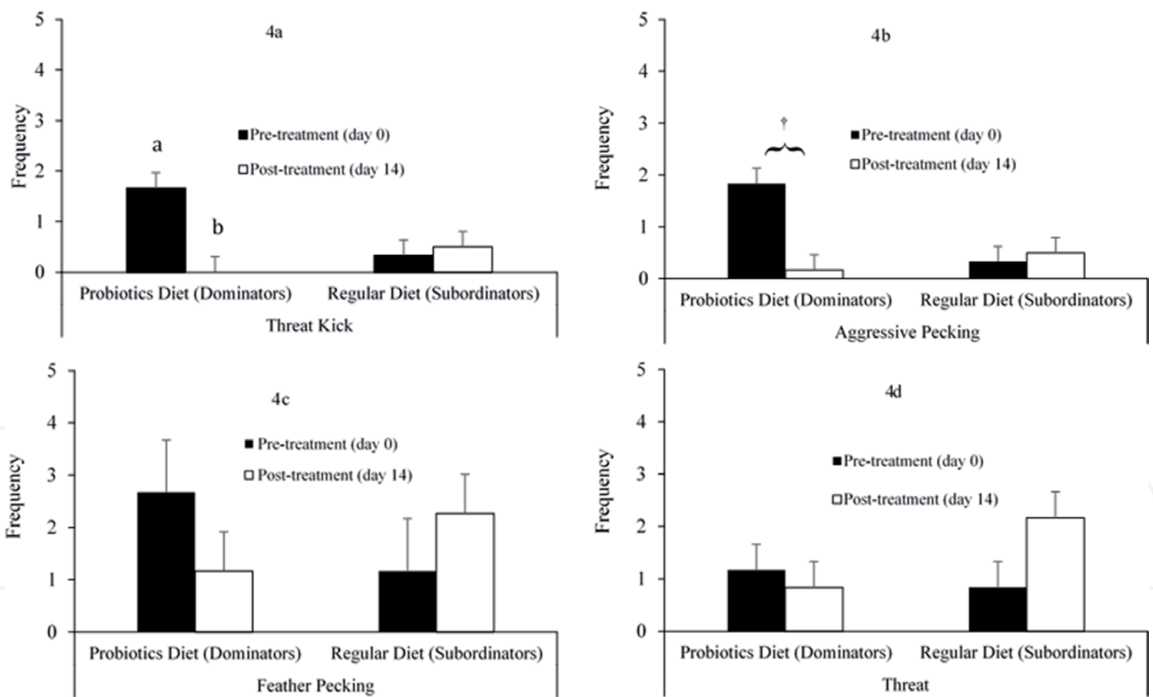


Figure 4. Frequency of aggressive behaviors at day 0 (pre-treatment) and day 14 (post-treatment) in probiotic fed hens and regular diet fed hens followed the paired social test. The exhibitions of aggressive behaviors in the regular diet fed subordinates were not affected by treatment ($P > 0.05$, respectively), while the frequency of threat kick ($P = 0.04$) was reduced, aggressive pecking ($P = 0.053$) was tend to be lower, and feather packing was declined (60%, $P = 0.33$) in probiotic fed dominantes post-treatment. Notes: the treatment effects on the measured behaviors were reversed between dominants and subordinates during the 2nd social rank test. ^{a,b} between the frequency at day 0 and day 14, least square means lacking common superscripts differ ($P < 0.05$); and [†] a trend difference ($0.05 \leq P < 0.10$).

In the current study, body weight gain and hen-day egg production were not affected in the probiotic fed hens compared with the regular diet fed control hens (Control = 2.83%, Probiotics = 2.2%, $P = 0.76$; Control = 73.6%, Probiotics = 87.5%,

$P = 0.18$, respectively). Previous studies have reported the beneficial effects of dietary supplementation of probiotics on daily weight gain, finished body weight, and feed conversion rate in broiler chickens [306, 307], turkeys [308], and swine [309]. Several studies also reported that probiotic diets improved egg production in hens [310]. The underlying mechanisms of these effects may be related to the beneficial bacterial growth in the gastrointestinal tract to facilitate the fermentation process which improves the digestion and utilization of nutrients in animals [311]. The beneficial effects on growth performance, however, are affected by the bacterial strains, preparation process, dosage, animal's age, and genetic type [312, 313]. In the current study, the probiotic was provided for 2 weeks only, which may not be sufficient to functionally improve both growth and production performance.

6. Conclusions

Our data suggest that dietary inclusion of probiotics has positive effects on reducing agonistic behaviors in laying hens through modification of the serotonergic system without negative effects on growth and production performance. The data indicate that dietary probiotic supplementation could be a useful management tool for preventing aggressive behaviors in laying hens. In addition, the current chicken strain could be a useful model to investigate mechanisms underlying the potentially probiotic therapy for preventing and reducing emotional susceptibility associated with psychiatric disorders such as depression and anxiety in humans.

Author details

Heng-Wei Cheng^{1*}, Sha Jiang² and Jiaying Hu³

1 USDA-Agricultural Research Service, Livestock Behavior Research Unit, West Lafayette, IN, USA

2 College of Animal Science and Technology, Southwest University, Chongqing, PR China

3 Department of Animal Sciences, Purdue University, West Lafayette, IN, USA

*Address all correspondence to: heng-wei.cheng@ars.usda.gov

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] De Almeida RM, Cabral JC, Narvaes R. Behavioural, hormonal and neurobiological mechanisms of aggressive behaviour in human and nonhuman primates. *Physiology & Behavior*. 2015;**143**:121-135
- [2] Arneth BM. Gut-brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: Gut dysbiosis and altered brain function. *Postgraduate Medical Journal*. 2018;**94**:446-452
- [3] Cusotto S, Sandhu KV, Dinan TG, Cryan JF. The neuroendocrinology of the microbiota-gut-brain axis: A behavioural perspective. *Frontiers in Neuroendocrinology*. 2018;**51**:80-101
- [4] Di Sabatino A, Lenti MV, Cammalleri L, Corazza GR, Pilotto A. Frailty and the gut. *Digestive and Liver Disease*. 2018;**50**(6):533-541
- [5] Farzi A, Fröhlich EE, Holzer P. Gut microbiota and the neuroendocrine system. *Neurotherapeutics*. 2018;**15**:5-22
- [6] Gerhardt S, Mohajeri MH. Changes of colonic bacterial composition in parkinson's disease and other neurodegenerative diseases. *Nutrients*. 2018;**10**. pii: E708
- [7] Liu L, Zhu G. Gut-brain axis and mood disorder. *Frontiers in Psychiatry*. 2018;**9**:223
- [8] Lyte JM. Probiotics function mechanistically as delivery vehicles for neuroactive compounds: Microbial endocrinology in the design and use of probiotics. *BioEssays*. 2011;**33**:574-581
- [9] Lyte JM. Eating for 3.8 × 10¹³: Examining the impact of diet and nutrition on the microbiota-gut-brain axis through the lens of microbial endocrinology. *Frontiers in Endocrinology*. 2019;**9**:796
- [10] Yang H, Duan Z. The local defender and functional mediator: Gut microbiome. *Digestion*. 2018;**97**:137-145
- [11] Bjerre K, Cantor MD, Nørgaard JV, Poulsen HD, Blaabjerg K, Canibe N, et al. Development of *Bacillus subtilis* mutants to produce tryptophan in pigs. *Biotechnology Letters*. 2017;**39**:289-295
- [12] Hussain S, Andrews D, Hill BC. Using tryptophan mutants to probe the structural and functional status of BsSCO, a copper binding, cytochrome c oxidase assembly protein from *Bacillus subtilis*. *Biochemistry*. 2017;**56**:6355-6367
- [13] Okada M, Sugita T, Abe I. Posttranslational isoprenylation of tryptophan in bacteria. *Beilstein Journal of Organic Chemistry*. 2017;**13**:338-346
- [14] Sheng QK, Yang ZJ, Zhao HB, Wang XL, Guo JF. Effects of L-tryptophan, fructan, and casein on reducing ammonia, hydrogen sulfide, and skatole in fermented swine manure. *Asian-Australasian Journal of Animal Sciences*. 2015;**28**:1202-1208
- [15] Chen S, Wang M, Yin L, Ren W, Bin P, Xia Y, et al. Effects of dietary tryptophan supplementation in the acetic acid-induced colitis mouse model. *Food & Function*. 2018;**9**:4143-4152
- [16] Gao J, Xu K, Liu H, Liu G, Bai M, Peng C, et al. Impact of the gut microbiota on intestinal immunity mediated by tryptophan metabolism. *Frontiers in Cellular and Infection Microbiology*. 2018;**8**:13
- [17] Mukhtar K, Nawaz H, Abid S. Functional gastrointestinal disorders and gut-brain axis: What does the future hold? *World Journal of Gastroenterology*. 2019;**25**:552-566
- [18] Wen H, Feng L, Jiang W, Liu Y, Jiang J, Li S, et al. Dietary tryptophan

modulates intestinal immune response, barrier function, antioxidant status and gene expression of TOR and Nrf2 in young grass carp (*Ctenopharyngodon idella*). *Fish & Shellfish Immunology*. 2014;**40**(1):275-287

[19] Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. *Current Opinion in Endocrinology, Diabetes, and Obesity*. 2013;**20**:14-21

[20] Pardridge WM, Fierer G. Transport of tryptophan into brain from the circulating, albumin-bound pool in rats and in rabbits. *Journal of Neurochemistry*. 1990;**54**:971-976

[21] de Boer SF, Buwalda B, Koolhaas JM. Untangling the neurobiology of coping styles in rodents: Towards neural mechanisms underlying individual differences in disease susceptibility. *Neuroscience & Biobehavioral Reviews*. 2017;**74**(Pt B):401-422

[22] Veroude K, Zhang-James Y, Fernández-Castillo N, Bakker MJ, Cormand B, Faraone SV. Genetics of aggressive behavior: An overview. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. 2016;**171B**(1):3-43

[23] Coccaro EF. What is the nature of serotonergic abnormalities in human aggression? *Biological Psychiatry*. 2012;**72**:980-981

[24] Dennis RL, Chen ZQ, Cheng HW. Serotonergic mediation of aggression in high and low aggressive chicken strains. *Poultry Science*. 2008;**87**:612-620

[25] Liu Y, Sun Y, Zhao X, Kim JY, Luo L, Wang Q, et al. Enhancement of aggression induced by isolation rearing is associated with a lack of central serotonin. *Neuroscience Bulletin*. 2019. <https://doi.org/10.1007/s12264-019-00373-w>

[26] Prokšelj T, Jerin A, Muck-Seler D, Kogoj A. Decreased platelet serotonin

concentration in Alzheimer's disease with involuntary emotional expression disorder. *Neuroscience Letters*. 2014;**578**:71-74

[27] Bharwani A, Mian MF, Surette MG, Bienenstock J, Forsythe P. Oral treatment with *Lactobacillus rhamnosus* attenuates behavioural deficits and immune changes in chronic social stress. *BMC Medicine*. 2017;**15**:7

[28] Latalova K, Hajda M, Prasko J. Can gut microbes play a role in mental disorders and their treatment? *Psychiatria Danubina*. 2017;**29**(1):28-30

[29] Marx W, Moseley G, Berk M, Jacka F. Nutritional psychiatry: The present state of the evidence. *The Proceedings of the Nutrition Society*. 2017;**76**:427-436

[30] Misra S, Mohanty D. Psychobiotics: A new approach for treating mental illness? *Critical Reviews in Food Science and Nutrition*. 2017;**30**:1-7

[31] Li B, Evivie SE, Lu J, Jiao Y, Wang C, Li Z, et al. *Lactobacillus helveticus* KLDS1.8701 alleviates D-galactose-induced aging by regulating Nrf-2 and gut microbiota in mice. *Food & Function*. 2018;**9**:6586-6598

[32] Li N, Wang Q, Wang Y, Sun A, Lin Y, Jin Y, et al. Oral probiotics ameliorate the behavioral deficits induced by chronic mild stress in mice via the gut microbiota-inflammation axis. *Frontiers in Behavioral Neuroscience*. 2018;**12**:266

[33] Bermúdez-Humarán LG, Salinas E, Ortiz GG, Ramirez-Jirano LJ, Morales JA, Bitzer-Quintero OK. From probiotics to psychobiotics: Live beneficial bacteria which act on the brain-gut axis. *Nutrients*. 2019;**11**. pii: E890

[34] Morris G, Fernandes BS, Puri BK, Walker AJ, Carvalho AF, Berk M. Leaky brain in neurological and psychiatric

disorders: Drivers and consequences. The Australian and New Zealand Journal of Psychiatry. 2018;52:924-948

[35] Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A. Mechanisms of action of probiotics. Advances in Nutrition. 2019;10(suppl_1):S49-S66

[36] Taylor AM, Holscher HD. A review of dietary and microbial connections to depression, anxiety, and stress. Nutritional Neuroscience. 2018;9:1-14

[37] Gomi A, Yamaji K, Watanabe O, Yoshioka M, Miyazaki K, Iwama Y, et al. *Bifidobacterium bifidum* YIT 10347 fermented milk exerts beneficial effects on gastrointestinal discomfort and symptoms in healthy adults: A double-blind, randomized, placebo-controlled study. Journal of Dairy Science. 2018;101:4830-4841

[38] Satish Kumar CS, Kondal Reddy K, Boobalan G, Gopala Reddy A, Sudha Rani Chowdhary CH, Vinoth A, et al. Immunomodulatory effects of *Bifidobacterium bifidum* 231 on trinitrobenzenesulfonic acid-induced ulcerative colitis in rats. Research in Veterinary Science. 2017;110:40-46

[39] Wang BG, Wu Y, Qiu L, Shah NP, Xu F, Wei H. Integration of genomic and proteomic data to identify candidate genes in HT-29 cells after incubation with *Bifidobacterium bifidum* ATCC 29521. Journal of Dairy Science. 2016;99(9):6874-6888

[40] Kim MJ, Ku S, Kim SY, Lee HH, Jin H, Kang S, et al. Safety evaluations of *Bifidobacterium bifidum* BGN4 and *Bifidobacterium longum* BORI. International Journal of Molecular Sciences. 2018;19. pii: E1422

[41] Kim N, Yun M, Oh YJ, Choi HJ. Mind-altering with the gut: Modulation of the gut-brain axis with probiotics. Journal of Microbiology. 2018;56:172-182

[42] Mauricio MD, Serna E, Fernández-Murga ML, Portero J, Aldasoro M, Valles SL, et al. *Bifidobacterium pseudocatenulatum* CECT 7765 supplementation restores altered vascular function in an experimental model of obese mice. International Journal of Medical Sciences. 2017;14:444-451

[43] Zhai Q, Liu Y, Wang C, Zhao J, Zhang H, Tian F, et al. Increased cadmium excretion due to oral administration of *Lactobacillus plantarum* strains by regulating enterohepatic circulation in mice. Journal of Agricultural and Food Chemistry. 2019;67:3956-3965

[44] Morita Y, Miwa Y, Jounai K, Fujiwara D, Kurihara T, Kanauchi O. *Lactobacillus paracasei* KW3110 prevents blue light-induced inflammation and degeneration in the retina. Nutrients. 2018;10. pii: E1991

[45] Orlando A, Linsalata M, Bianco G, Notarnicola M, D'Attoma B, Scavo MP, et al. *Lactobacillus rhamnosus* GG protects the epithelial barrier of Wistar rats from the pepsin-trypsin-digested gliadin (PTG)-induced enteropathy. Nutrients. 2018;10(11). pii: E1698

[46] Kato M, Hamazaki Y, Sun S, Nishikawa Y, Kage-Nakadai E. *Clostridium butyricum* MIYAIRI 588 increases the lifespan and multiple-stress resistance of *Caenorhabditis elegans*. Nutrients. 2018;10. pii: E1921. DOI: 10.3390/nu10121921

[47] Eom T, Kim YS, Choi CH, Sadowsky MJ, Unno T. Current understanding of microbiota- and dietary-therapies for treating inflammatory bowel disease. Journal of Microbiology. 2018;56:189-198

[48] Silley P. Do bacteria need to be regulated? Journal of Applied Microbiology. 2006;101:607-615

- [49] Joerger RD, Ganguly A. Current status of the preharvest application of pro- and prebiotics to farm animals to enhance the microbial safety of animal products. *Microbiology Spectrum*. 2017;**5**:1-10
- [50] De Baets L, Van Iwaarden P, Meeus N, Schimmel H, Philipp W, Emons H. First certified reference materials for molecular fingerprinting of two approved probiotic *Bacillus* strains. *International Journal of Food Microbiology*. 2009;**129**:16-20
- [51] Isticato R, Ricca E. Spore surface display. *Microbiology Spectrum*. 2014;**2**(5):1-15
- [52] Jeżewska-Frąckowiak J, Seroczyńska K, Banaszczyk J, Jedrzejczak G, Żylicz-Stachula A, Skowron PM. The promises and risks of probiotic *Bacillus* species. *Acta Biochimica Polonica*. 2018;**65**:509-519
- [53] Goodarzi Boroojeni F, Vahjen W, Männer K, Blanch A, Sandvang D, Zentek J. *Bacillus subtilis* in broiler diets with different levels of energy and protein. *Poultry Science*. 2018;**97**:3967-3976
- [54] Musa BB, Duan Y, Khawar H, Sun Q, Ren Z, Elsiddig Mohamed MA, et al. *Bacillus subtilis* B21 and *Bacillus licheniformis* B26 improve intestinal health and performance of broiler chickens with *Clostridium perfringens*-induced necrotic enteritis. *Journal of Animal Physiology and Animal Nutrition*. 2019;00:1-11. <https://doi.org/10.1111/jpn.13082>
- [55] Upadhaya SD, Rudeaux F, Kim IH. Effects of inclusion of *Bacillus subtilis* (Gallipro) to energy- and protein-reduced diet on growth performance, nutrient digestibility, and meat quality and gas emission in broilers. *Poultry Science*. 2019;**98**(5):2169-2178
- [56] Samanya M, Yamauchi K. Histological alterations of intestinal villi in chickens fed dried *Bacillus subtilis* var. *natto*. *Comparative Biochemistry and Physiology. Part A, Molecular & Integrative Physiology*. 2002;**133**:95-104
- [57] Bar Shira E, Friedman A. Innate immune functions of avian intestinal epithelial cells: Response to bacterial stimuli and localization of responding cells in the developing avian digestive tract. *PLoS One*. 2018;**13**:e0200393
- [58] Fernandez-Alarcon MF, Trottier N, Steibel JP, Lunedo R, Campos DMB, Santana AM, et al. Interference of age and supplementation of direct-fed microbial and essential oil in the activity of digestive enzymes and expression of genes related to transport and digestion of carbohydrates and proteins in the small intestine of broilers. *Poultry Science*. 2017;**96**:2920-2930
- [59] Gadde U, Oh ST, Lee YS, Davis E, Zimmerman N, Rehberger T, et al. The effects of direct-fed microbial supplementation, as an alternative to antibiotics, on growth performance, intestinal immune status, and epithelial barrier gene expression in broiler chickens. *Probiotics and Antimicrobial Proteins*. 2017;**9**:397-405
- [60] Jayaraman S, Das PP, Saini PC, Roy B, Chatterjee PN. Use of *Bacillus subtilis* PB6 as a potential antibiotic growth promoter replacement in improving performance of broiler birds. *Poultry Science*. 2017;**96**:2614-2622
- [61] Abudabos AM, Hussein EOS, Ali MH, Al-Ghadi MQ. The effect of some natural alternative to antibiotics on growth and changes in intestinal histology in broiler exposed to *Salmonella* challenge. *Poultry Science*. 2019;**98**:1441-1446
- [62] Wang YQ, Lin WW, Wu N, Wang SY, Chen MZ, Lin ZH, et al. Structural insight into the serotonin (5-HT)

receptor family by molecular docking, molecular dynamics simulation and systems pharmacology analysis. *Acta Pharmacologica Sinica*. 2019. DOI: 10.1038/s41401-019-0217-9

[63] Wang X, Peebles ED, Kiess AS, Wamsley KGS, Zhai W. Effects of coccidial vaccination and dietary antimicrobial alternatives on the growth performance, internal organ development, and intestinal morphology of *Eimeria*-challenged male broilers. *Poultry Science*. 2019;**98**(5):2054-2065

[64] Galagarza OA, Smith SA, Drahos DJ, Eifert JD, Williams RC, Kuhn DD. Modulation of innate immunity in Nile tilapia (*Oreochromis niloticus*) by dietary supplementation of *Bacillus subtilis* endospores. *Fish and Shellfish Immunology*. 2018;**83**:171-179

[65] Fan Y, Zhao L, Ma Q, Li X, Shi H, Zhou T, et al. Effects of *Bacillus subtilis* ANSB060 on growth performance, meat quality and aflatoxin residues in broilers fed moldy peanut meal naturally contaminated with aflatoxins. *Food and Chemical Toxicology*. 2013;**59**:748-753

[66] Gong L, Wang B, Mei X, Xu H, Qin Y, Li W, et al. Effects of three probiotic *Bacillus* on growth performance, digestive enzyme activities, antioxidative capacity, serum immunity, and biochemical parameters in broilers. *Animal Science Journal*. 2018;**89**:1561-1571

[67] Wang WC, Yan FF, Hu JY, Huang XH, Kamel OM, Cheng HW. Supplementation of *Bacillus subtilis* based probiotic reduces heat stress-related behaviors and inflammatory response in broiler chickens. *Journal of Animal Science*. 2018;**96**:1654-1666

[68] Zaghar M, Zahroojian N, Riahi M, Parhizkar S. Effect of *Bacillus Subtilis* Spore (GalliPro) nutrients equivalency value on broiler chicken performance.

Italian Journal of Animal Science. 2015;**14**:94-98

[69] Sarsero JP, Merino E, Yanofsky C. A *Bacillus subtilis* operon containing genes of unknown function senses tRNA^{Trp} charging and regulates expression of the genes of tryptophan biosynthesis. *Proceedings of the National Academy of Sciences of the United States of America*. 2000;**97**:2656-2661

[70] Gollnick P, Babitzke P, Antson A, Yanofsky C. Regulation of sigL expression by the catabolite control protein CcpA involves a roadblock mechanism in *Bacillus subtilis*: Potential connection between carbon and nitrogen metabolism. *Annual Review of Genetics*. 2005;**39**:47-68

[71] Porter MR, Joyce PR, Luty SE. Tryptophan and tyrosine availability and response to antidepressant treatment in major depression. *Journal of Affective Disorders*. 2005;**86**:129-134

[72] van Veen JF, van Vliet IM, de Rijk RH, van Pelt J, Mertens B, Fekkes D, et al. Tryptophan depletion affects the autonomic stress response in generalized social anxiety disorder. *Psychoneuroendocrinology*. 2009;**34**:1590-1594

[73] Aune TM, Pogue SL. Inhibition of tumor cell growth by interferon-gamma is mediated by two distinct mechanisms dependent upon oxygen tension: Induction of tryptophan degradation and depletion of intracellular nicotinamide adenine dinucleotide. *The Journal of Clinical Investigation*. 1989;**84**:863-875

[74] Frank DN, St Amand AL, Feldman RA. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;**104**:13780-13785

- [75] O'Callaghan TF, Ross RP, Stanton C, Clarke G. The gut microbiome as a virtual endocrine organ with implications for farm and domestic animal endocrinology. *Domestic Animal Endocrinology*. 2016;**56**(Suppl):S44-S55
- [76] Jia Q, Xie Y, Lu C, Zhang A, Lu Y, Lv S, et al. Endocrine organs of cardiovascular diseases: Gut microbiota. *Journal of Cellular and Molecular Medicine*. 2019;**23**:2314-2323
- [77] Lach G, Schellekens H, Dinan TG, Cryan JF. Anxiety, depression, and the microbiome: A role for gut peptides. *Neurotherapeutics*. 2018;**15**:36-59
- [78] Villageliu DN, Lyte M. Microbial endocrinology: Why the intersection of microbiology and neurobiology matters to poultry health. *Poultry Science*. 2017;**96**:2501-2508
- [79] Yarandi SS, Peterson DA, Treisman GJ, Moran TH, Pasricha PJ. Modulatory effects of gut microbiota on the central nervous system: How gut could play a role in neuropsychiatric health and Diseases. *Journal of Neurogastroenterology and Motility*. 2016;**22**:201-212
- [80] Cheung SG, Goldenthal AR, Uhlemann AC, Mann JJ, Miller JM, Sublette ME. Systematic review of gut microbiota and major depression. *Frontiers in Psychiatry*. 2019;**10**:34
- [81] Huang TT, Lai JB, Du YL, Xu Y, Ruan LM, Hu SH. Current understanding of gut microbiota in mood disorders: An update of human studies. *Frontiers in Genetics*. 2019;**10**:98
- [82] Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: The gut-brain axis. *Journal of Neuroinflammation*. 2019;**16**:53
- [83] Molina-Torres G, Rodriguez-Arrastia M, Roman P, Sanchez-Labraca N, Cardona D. Stress and the gut microbiota-brain axis. *Behavioural Pharmacology*. 2019;**30**(2 and 3—special issue):187-200
- [84] Gao K, Pi Y, Mu CL, Farzi A, Liu Z, Zhu WY. Increasing carbohydrate availability in the hindgut promotes hypothalamic neurotransmitter synthesis: Aromatic amino acids linking the microbiota-brain axis. *Journal of Neurochemistry*. 2019;**149**:641-659
- [85] Jameson KG, Hsiao EY. Linking the gut microbiota to a brain neurotransmitter. *Trends in Neurosciences*. 2018;**41**:413-414
- [86] Martin CR, Osadchiy V, Kalani A, Mayer EA. The brain-gut-microbiome axis. *Cellular and Molecular Gastroenterology and Hepatology*. 2018;**6**:133-148
- [87] Strandwitz P. Neurotransmitter modulation by the gut microbiota. *Brain Research*. 2018;**1693**(Pt B):128-133
- [88] O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. *Behavioural Brain Research*. 2015;**277**:32-48
- [89] Jenkins TA, Nguyen JC, Polglaze KE, Bertrand PP. Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. *Nutrients*. 2016;**8**. pii: E56. DOI: 10.3390/nu8010056
- [90] Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Kynurenine pathway metabolism and the microbiota-gut-brain axis. *Neuropharmacology*. 2017;**112**(Pt B):399-412
- [91] Browne CJ, Abela AR, Chu D, Li Z, Ji X, Lambe EK, et al. Dorsal raphe serotonin neurons inhibit operant responding for reward via inputs to the ventral tegmental area but

not the nucleus accumbens: Evidence from studies combining optogenetic stimulation and serotonin reuptake inhibition. *Neuropsychopharmacology*. 2019;**44**:793-804

[92] Pratelli M, Pasqualetti M. Serotonergic neurotransmission manipulation for the understanding of brain development and function: Learning from Tph2 genetic models. *Biochimie*. 2018;**161**:3-14

[93] Revill AL, Chu NY, Ma L, LeBlancq MJ, Dickson CT, Funk GD. Postnatal development of persistent inward currents in rat XII motoneurons and their modulation by serotonin, muscarine and norepinephrine. *The Journal of Physiology*. 2019. DOI: 10.1113/JP277572

[94] Warner BB. The contribution of the gut microbiome to neurodevelopment and neuropsychiatric disorders. *Pediatric Research*. 2018;**85**:216-224

[95] Needham BD, Tang W, Wu WL. Searching for the gut microbial contributing factors to social behavior in rodent models of autism spectrum disorder. *Developmental Neurobiology*. 2018;**78**:474-499

[96] Reales G, Paixão-Côrtés VR, Cybis GB, Gonçalves GL, Pissinatti A, Salzano FM, et al. Serotonin, behavior, and natural selection in New World monkeys. *Journal of Evolutionary Biology*. 2018;**31**:1180-1192

[97] Conio B, Martino M, Magioncalda P, Escelsior A, Inglese M, Amore M, et al. Opposite effects of dopamine and serotonin on resting-state networks: Review and implications for psychiatric disorders. *Molecular Psychiatry*. 2019. DOI: 10.1038/s41380-019-0406-4

[98] Dinan TG, Cryan JF. Brain-gut-microbiota axis and mental health. *Psychosomatic Medicine*. 2017;**79**:920-926

[99] Sirgy MJ. Positive balance: A hierarchical perspective of positive mental health. *Quality of Life Research*. 2019. <https://doi.org/10.1007/s11136-019-02145-5>

[100] Sjögren M, Nielsen ASM, Hasselbalch KC, Wøllo M, Hansen JS. A systematic review of blood-based serotonergic biomarkers in Bulimia Nervosa. *Psychiatry Research*. 2018. <https://doi.org/10.1016/j.psychres.2018.12.16>

[101] Cameron JL, Eagleson KL, Fox NA, Hensch TK, Levitt P. Social origins of developmental risk for mental and physical illness. *The Journal of Neuroscience*. 2017;**37**(45):10783-10791

[102] Fahey AG, Cheng HW. Effects of social disruption on physical parameters, corticosterone concentrations, and immune system in two genetic lines of White Leghorn layers. *Poultry Science*. 2008;**87**:1947-1954

[103] Mumtaz F, Khan MI, Zubair M, Dehpour AR. Neurobiology and consequences of social isolation stress in animal model—A comprehensive review. *Biomedicine & Pharmacotherapy*. 2018;**105**:1205-1222

[104] Kleinhappel TK, John EA, Pike TW, Wilkinson A, Burman OH. Animal welfare: A social networks perspective. *Science Progress*. 2016;**99**:68-82

[105] Lin ED, Sun M, Choi EY, Magee D, Stets C, During MJ. Social overcrowding as a chronic stress model that increases adiposity in mice. *Psychoneuroendocrinology*. 2015;**51**:318-330

[106] Mench JA. The welfare of poultry in modern production system. *Poultry Science Reviews*. 1992;**4**:107-123

[107] Escribano D, Ko HL, Chong Q, Llonch L, Manteca X, Llonch P. Salivary

biomarkers to monitor stress due to aggression after weaning in piglets. *Research in Veterinary Science*. 2019;**123**:178-183

[108] Haller J. The role of the lateral hypothalamus in violent intraspecific aggression—The glucocorticoid deficit hypothesis. *Frontiers in Systems Neuroscience*. 2018;**12**:26

[109] Masis-Calvo M, Schmidtner AK, de Moura Oliveira VE, Grossmann CP, de Jong TR, Neumann ID. Animal models of social stress: The dark side of social interactions. *Stress*. 2018;**10**:1-16

[110] de Bruijn R, Romero LM. The role of glucocorticoids in the vertebrate response to weather. *General and Comparative Endocrinology*. 2018;**269**:11-32

[111] Haller J, Millar S, van de Schraaf J, de Kloet RE, Kruk MR. The active phase-related increase in corticosterone and aggression are linked. *Journal of Neuroendocrinology*. 2000;**12**:431-436

[112] Vitellius G, Trabado S, Bouligand J, Delemer B, Lombès M. Pathophysiology of Glucocorticoid Signaling. *Annales d'endocrinologie*. 2018;**79**:98-106

[113] Désautés C, Sarrieau A, Caritez JC, Mormède P. Behavior and pituitary-adrenal function in large white and Meishan pigs. *Domestic Animal Endocrinology*. 1999;**16**:193-205

[114] Reynolds RM. Glucocorticoid excess and the developmental origins of disease: Two decades of testing the hypothesis—2012 Curt Richter Award Winner. *Psychoneuroendocrinology*. 2013;**38**:1-11

[115] Joëls M, Karst H, Sarabdjitsingh RA. The stressed brain of humans and rodents. *Acta Physiologica (Oxford, England)*. 2018;**223**(2):e13066

[116] Peeters B, Langouche L, Van den Berghe G. Adrenocortical stress

response during the course of critical illness. *Comprehensive Physiology*. 2017;**8**:283-298

[117] Ralph CR, Tilbrook AJ. Invited review: The usefulness of measuring glucocorticoids for assessing animal welfare. *Journal of Animal Science*. 2016;**94**:457-470

[118] Carpenter RE, Korzan WJ, Bockholt C, Watt MJ, Forster GL, Renner KJ, et al. Corticotropin releasing factor influences aggression and monoamines: Modulation of attacks and retreats. *Neuroscience*. 2009;**158**:412-425

[119] Fortes PM, Albrechet-Souza L, Vasconcelos M, Ascoli BM, Menegolla AP, de Almeida RMM. Social instigation and repeated aggressive confrontations in male Swiss mice: Analysis of plasma corticosterone, CRF and BDNF levels in limbic brain areas. *Trends in Psychiatry and Psychotherapy*. 2017;**39**:98-105

[120] Kinlein SA, Phillips DJ, Keller CR, Karatsoreos IN. Role of corticosterone in altered neurobehavioral responses to acute stress in a model of compromised hypothalamic-pituitary-adrenal axis function. *Psychoneuroendocrinology*. 2019;**102**:248-255

[121] Reul JM, de Kloet ER. Two receptor systems for corticosterone in rat brain: Microdistribution and differential occupation. *Endocrinology*. 1985;**117**:2505-2511

[122] Algamal M, Ojo JO, Lungmus CP, Muza P, Cammarata C, Owens MJ, et al. Chronic hippocampal abnormalities and blunted HPA axis in an animal model of repeated unpredictable stress. *Frontiers in Behavioral Neuroscience*. 2018;**12**:150

[123] Ahmed AA, Ma W, Ni Y, Wang S, Zhao R. Corticosterone in ovo modifies aggressive behaviors and reproductive

performances through alterations of the hypothalamic-pituitary-gonadal axis in the chicken. *Animal Reproduction Science*. 2014;**146**:193-201

[124] Audet MC, McQuaid RJ, Merali Z, Anisman H. Cytokine variations and mood disorders: Influence of social stressors and social support. *Frontiers in Neuroscience*. 2014;**8**:416

[125] Walker SE, Papilloud A, Huzard D, Sandi C. The link between aberrant hypothalamic-pituitary-adrenal axis activity during development and the emergence of aggression—Animal studies. *Neuroscience and Biobehavioral Reviews*. 2018;**91**:138-152

[126] Veenit V, Cordero MI, Tzanoulinou S, Sandi C. Increased corticosterone in peripubertal rats leads to long-lasting alterations in social exploration and aggression. *Frontiers in Behavioral Neuroscience*. 2013;**7**:26

[127] Foster JA, McVey Neufeld KA. Gut-brain axis: How the microbiome influences anxiety and depression. *Trends in Neurosciences*. 2013;**36**:305-312

[128] Walker SE, Sandi C. Long-term programming of psychopathology-like behaviors in male rats by peripubertal stress depends on individual's glucocorticoid responsiveness to stress. *Stress*. 2018;**7**:1-10

[129] Cant MA, Llop JB, Field J. Individual variation in social aggression and the probability of inheritance: Theory and a field test. *The American Naturalist*. 2006;**167**:837-852

[130] Foister S, Doeschl-Wilson A, Roehre R, Arnott G, Boyle L, Turner S. Social network properties predict chronic aggression in commercial pig systems. *PLoS One*. 2018;**13**:e0205122

[131] Greenwood EC, van Wettere WHEJ, Rayner J, Hughes PE, Plush KL.

Provision point-source materials stimulates play in sows but does not affect aggression at regrouping. *Animals (Basel)*. 2019;**9**(1): pii: E8. DOI: 10.3390/ani9010008

[132] Cheng HW. Breeding of tomorrow's chickens to improve well-being. *Poultry Science*. 2010;**89**:805-813

[133] Rauw WM, Johnson AK, Gomez-Raya L, Dekkers JCM. A hypothesis and review of the relationship between selection for improved production efficiency, coping behavior, and domestication. *Frontiers in Genetics*. 2017;**8**:134

[134] Brimblecombe N, Evans-Lacko S, Knapp M, King D, Takizawa R, Maughan B, et al. Long term economic impact associated with childhood bullying victimisation. *Social Science & Medicine*. 2018;**208**:134-141

[135] Ramsay SE, Bartley A, Rodger AJ. Determinants of assault-related violence in the community: Potential for public health interventions in hospitals. *Emergency Medicine Journal*. 2014;**31**:986-989

[136] Whitaker S. Preventing violent conflict: A revised mandate for the public health professional? *Journal of Public Health Policy*. 2013;**34**:46-54

[137] Bruce-Keller AJ, Salbaum JM, Berthoud HR. Harnessing gut microbes for mental health: Getting from here to there. *Biological Psychiatry*. 2018;**83**:214-223

[138] Rieder R, Wisniewski PJ, Alderman BL, Campbell SC. Microbes and mental health: A review. *Brain, Behavior, and Immunity*. 2017;**66**:9-17

[139] Sylvia KE, Demas GE. A gut feeling: Microbiome-brain-immune interactions modulate social and affective behaviors. *Hormones and Behavior*. 2018;**99**:41-49

- [140] Lin L, Zhang J. Role of intestinal microbiota and metabolites on gut homeostasis and human diseases. *BMC Immunology*. 2017;**18**:2
- [141] Pickard JM, Zeng MY, Caruso R, Núñez G. Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. *Immunological Reviews*. 2017;**279**:70-89
- [142] Berman S, Petriz B, Kajėnienė A, Prestes J, Castell L, Franco OL. The microbiota: An exercise immunology perspective. *Exercise Immunology Review*. 2015;**21**:70-79
- [143] Bruce-Keller AJ, Salbaum JM, Luo M, Blanchard E, Taylor CM, Welsh DA, et al. Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biological Psychiatry*. 2015;**77**:607-615
- [144] Lallès JP. Microbiota-host interplay at the gut epithelial level, health and nutrition. *Journal of Animal Science and Biotechnology*. 2016;**7**:66
- [145] Delaney S, Hornig M. Environmental exposures and neuropsychiatric disorders: What role does the gut-immune-brain axis play? *Current Environmental Health Reports*. 2018;**5**:158-169
- [146] Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *The Journal of Physiology*. 2004;**558**:263-275
- [147] Cryan JF, Dinan TG. Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nature Reviews. Neuroscience*. 2012;**13**:701-712
- [148] Clarke G, Stilling RM, Kennedy PJ, Stanton C, Cryan JF, Dinan TG. Minireview: Gut microbiota: The neglected endocrine organ. *Molecular Endocrinology*. 2014;**28**:1221-1238
- [149] Maddaloni G, Migliarini S, Napolitano F, Giorgi A, Nazzi S, Biasci D, et al. Serotonin depletion causes valproate-responsive manic-like condition and increased hippocampal neuroplasticity that are reversed by stress. *Scientific Reports*. 2018;**8**:11847
- [150] Manchia M, Carpiello B, Valtorta F, Comai S. Serotonin dysfunction, aggressive behavior, and mental illness: Exploring the link using a dimensional approach. *ACS Chemical Neuroscience*. 2017;**8**:961-972
- [151] Birkel P, Franke L, Bas Rodenburg T, Ellen E, Harlander-Matauschek A. A role for plasma aromatic amino acids in injurious pecking behavior in laying hens. *Physiology & Behavior*. 2017;**175**:88-96
- [152] Cheng HW, Dillworth G, Singleton P, Chen Y, Muir WM. Effects of group selection for productivity and longevity on blood concentrations of serotonin, catecholamine and corticosterone of laying hens. *Poultry Science*. 2001;**80**:1278-1285
- [153] de Haas EN, van der Eijk JA. Where in the serotonergic system does it go wrong? Unravelling the route by which the serotonergic system affects feather pecking in chickens. *Neuroscience and Biobehavioral Reviews*. 2018;**95**:170-188
- [154] Dennis RL, Fahey AG, Cheng HW. Alterations to embryonic serotonin change aggression and fearfulness. *Aggressive Behavior*. 2013;**39**:91-98
- [155] Lesch KP, Araragi N, Waider J, van den Hove D, Gutknecht L. Targeting brain serotonin synthesis: Insights into neurodevelopmental disorders with long-term outcomes related to negative emotionality, aggression and antisocial behaviour. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. 2012;**367**:2426-2443

- [156] Olivier B. Serotonergic mechanisms in aggression. Novartis Foundation symposium. 2005;**268**:171-183; discussion 183-179, 242-153
- [157] Olivier B. Serotonin: A never-ending story. European Journal of Pharmacology. 2015;**753**:2-18
- [158] Reif A, Lesch KP. Toward a molecular architecture of personality. Behavioural Brain Research. 2003;**139**:1-20
- [159] Bubak AN, Watt MJ, Renner KJ, Luman AA, Costabile JD, Sanders EJ, et al. Sex differences in aggression: Differential roles of 5-HT₂, neuropeptide F and tachykinin. PLoS One. 2019;**14**(1):e0203980
- [160] Godar SC, Mosher LJ, Scheggi S, Devoto P, Moench KM, Strathman HJ, et al. Gene-environment interactions in antisocial behavior are mediated by early-life 5-HT_{2A} receptor activation. Neuropsychopharmacology. 2019. <https://doi.org/10.1016/j.neuropharm.2019.01.028>
- [161] Popova NK, Naumenko VS, Plyusnina IZ. Involvement of brain serotonin 5-HT_{1A} receptors in genetic predisposition to aggressive behavior. Neuroscience and Behavioral Physiology. 2007;**37**:631-635
- [162] van Hierden YM, Korte SM, Ruesink EW, van Reenen CG, Engel B, Korte-Bouws GA, et al. Adrenocortical reactivity and central serotonin and dopamine turnover in young chicks from a high and low feather-pecking line of laying hens. Physiology & Behavior. 2002;**75**:653-659
- [163] Wright HF, Mills DS, Pollux PM. Behavioural and physiological correlates of impulsivity in the domestic dog (*Canis familiaris*). Physiology & Behavior. 2012;**105**:676-682
- [164] Klasen M, Wolf D, Eisner PD, Eggermann T, Zerres K, Zepf FD, et al. Serotonergic contributions to human brain aggression networks. Frontiers in Neuroscience. 2019;**13**:42
- [165] Kolla NJ, Houle S. Single-photon emission computed tomography and positron emission tomography studies of antisocial personality disorder and aggression: A targeted review. Current Psychiatry Reports. 2019;**21**:24
- [166] Weinberg-Wolf H, Chang SWC. Differences in how macaques monitor others: Does serotonin play a central role? Wiley Interdisciplinary Reviews: Cognitive Science. 2019;**18**:e1494. DOI: 10.1002/wcs
- [167] Kästner N, Richter SH, Urbanik S, Kunert J, Waider J, Lesch KP, et al. Brain serotonin deficiency affects female aggression. Scientific Reports. 2019;**9**:1366
- [168] Cheng HW, Muir WM. Mechanisms of aggression and production in chickens: Genetic variations in the functions of serotonin, catecholamine, and corticosterone. World's Poultry Science Journal. 2007;**63**:233-254
- [169] Veenema AH. Early life stress, the development of aggression and neuroendocrine and neurobiological correlates: What can we learn from animal models? Frontiers in Neuroendocrinology. 2009;**30**:497-518
- [170] Melloni RH Jr, Ricci LA. Adolescent exposure to anabolic/androgenic steroids and the neurobiology of offensive aggression: A hypothalamic neural model based on findings in pubertal Syrian hamsters. Hormones and Behavior. 2010;**58**(1):177-191
- [171] Haller J. The neurobiology of abnormal manifestations of aggression—A review of hypothalamic mechanisms in cats, rodents, and humans. Brain Research Bulletin. 2013;**93**:97-109

- [172] Nikulina EM. Neural control predatory aggression in wild and domesticated animals. *Neuroscience & Biobehavioral Reviews*. 1991;**15**:545-547
- [173] Tani Y, Kataoka Y, Sakurai Y, Yamashita K, Ushio M, Ueki S. Changes of brain monoamine contents in three models of experimentally induced muricide in rats. *Pharmacology, Biochemistry, and Behavior*. 1987;**26**:725-729
- [174] Ferris CF, Stolberg T, Delville Y. Serotonin regulation of aggressive behavior in male golden hamsters (*Mesocricetus auratus*). *Behavioral Neuroscience*. 1999;**113**:804-815
- [175] Levinstein MR, Neumaier JF. Striatal 5-HT_{1B} receptors and aggression. *Biological Psychiatry*. 2017;**82**:235-236
- [176] Nautiyal KM, Tanaka KF, Barr MM, Tritschler L, Le Dantec Y, David DJ, et al. Distinct circuits underlie the effects of 5-HT_{1B} receptors on aggression and impulsivity. *Neuron*. 2015;**86**:813-826
- [177] Köhler S, Cierpinsky K, Kronenberg G, Adli M. The serotonergic system in the neurobiology of depression: Relevance for novel antidepressants. *Journal of Psychopharmacology*. 2016;**30**:13-22
- [178] Berman ME, McCloskey MS, Fanning JR, Schumacher JA, Coccaro EF. Serotonin augmentation reduces response to attack in aggressive individuals. *Psychological Science*. 2009;**20**:714-720
- [179] Fanning JR, Berman ME, Guillot CR, Marsic A, McCloskey MS. Serotonin (5-HT) augmentation reduces provoked aggression associated with primary psychopathy traits. *Journal of Personality Disorders*. 2014;**28**:449-461
- [180] Moffitt TE, Brammer GL, Caspi A, Fawcett JP, Raleigh M, Yuwiler A, et al. Whole blood serotonin relates to violence in an epidemiological study. *Biological Psychiatry*. 1998;**43**:446-457
- [181] Rosado B, Garcia-Belenguer S, Leon M, Chacon G, Villegas A, Palacio J. Effect of fluoxetine on blood concentrations of serotonin, cortisol and dehydroepiandrosterone in canine aggression. *Journal of Veterinary Pharmacology and Therapeutics*. 2011;**34**:430-436
- [182] Laricchiuta D, Petrosini L. Individual differences in response to positive and negative stimuli: Endocannabinoid-based insight on approach and avoidance behaviors. *Frontiers in Systems Neuroscience*. 2014;**8**:238
- [183] Petrican R, Grady CL. The intrinsic neural architecture of inhibitory control: The role of development and emotional experience. *Neuropsychologia*. 2019;**127**:93-105
- [184] Palumbo S, Mariotti V, Iofrida C, Pellegrini S. Genes and aggressive behavior: Epigenetic mechanisms underlying individual susceptibility to aversive environments. *Frontiers in Behavioral Neuroscience*. 2018;**12**:117
- [185] Ettrup KS, Sørensen JC, Rodell A, Alstrup AK, Bjarkam CR. Hypothalamic deep brain stimulation influences autonomic and limbic circuitry involved in the regulation of aggression and cardiocerebrovascular control in the Göttingen minipig. *Stereotactic and Functional Neurosurgery*. 2012;**90**:281-291
- [186] Johnsson M, Williams MJ, Jensen P, Wright D. Genetical genomics of behavior: A novel chicken genomic model for anxiety behavior. *Genetics*. 2016;**202**:327-340
- [187] Stern CD. The chick; a great model system becomes even greater. *Developmental Cell*. 2005;**8**:9-17

- [188] Goodson JL. The vertebrate social behavior network: Evolutionary themes and variations. *Hormones and Behavior*. 2005;**48**:11-22
- [189] Kuenzel WJ. Research advances made in the avian brain and their relevance to poultry scientists. *Poultry Science*. 2014;**93**:2945-2952
- [190] Kuenzel WJ. Mapping the brain of the chicken (*Gallus gallus*), with emphasis on the septal-hypothalamic region. *General and Comparative Endocrinology*. 2018;**256**:4-15
- [191] Soma KK, Bindra RK, Gee J, Wingfield JC, Schlinger BA. Androgen-metabolizing enzymes show region-specific changes across the breeding season in the brain of a wild songbird. *Journal of Neurobiology*. 1999;**41**:176-188
- [192] Thompson RR, Goodson JL, Ruscio MG, Adkins-Regan E. Role of the archistriatal nucleus taeniae in the sexual behavior of male Japanese quail (*Coturnix japonica*): A comparison of function with the medial nucleus of the amygdala in mammals. *Brain, Behavior and Evolution*. 1998;**51**:215-229
- [193] Challet E, Miceli D, Pierre J, Reperant J, Masicotte G, Herbin M, et al. Distribution of serotonin-immunoreactivity in the brain of the pigeon (*Columba livia*). *Anatomy and Embryology*. 1996;**193**:209-227
- [194] Butler AB. Evolution of brains, cognition, and consciousness. *Brain Research Bulletin*. 2008;**75**:442-449
- [195] Tramontin AD, Brenowitz EA. Seasonal plasticity in the adult brain. *Trends in Neurosciences*. 2000;**23**:251-258
- [196] Dietl MM, Palacios JM. Neurotransmitter receptors in the avian brain. I. Dopamine receptors. *Brain Research*. 1988;**439**:354-359
- [197] Walker EA, Yamamoto T, Hollingsworth PJ, Smith CB, Woods JH. Discriminative-stimulus effects of quipazine and l-5-hydroxytryptophan in relation to serotonin binding sites in the pigeon. *The Journal of Pharmacology and Experimental Therapeutics*. 1991;**259**:772-782
- [198] Savory CJ, Mann JS. Feather pecking in groups of growing bantams in relation to floor litter substrate and plumage colour. *British Poultry Science*. 1999;**40**:565-572
- [199] Smulders TV. The avian hippocampal formation and the stress response. *Brain, Behavior and Evolution*. 2017;**90**(1):81-91
- [200] Ottaviani E, Franchini A, Franceschi C. Presence of immunoreactive corticotropin-releasing hormone and cortisol molecules in invertebrate haemocytes and lower and higher vertebrate thymus. *The Histochemical Journal*. 1998;**30**:61-67
- [201] Carsia RV, Macdonald GJ, Malamed S. Steroid control of steroidogenesis in isolated adrenocortical cells: Molecular and species specificity. *Steroids*. 1983;**41**:741-755
- [202] Palme R, Rettenbacher S, Touma C, El-Bahr SM, Möstl E. Stress hormones in mammals and birds: Comparative aspects regarding metabolism, excretion, and noninvasive measurement in fecal samples. *Annals of the New York Academy of Sciences*. 2005;**1040**:162-171
- [203] Vylitová M, Miksík I, Pácha J. Metabolism of corticosterone in mammalian and avian intestine. *General and Comparative Endocrinology*. 1998;**109**:315-324
- [204] Stange M, Núñez-León D, Sánchez-Villagra MR, Jensen P, Wilson LAB. Morphological variation under

domestication: How variable are chickens? Royal Society Open Science. 2018;**5**:180993

[205] Cheng HW. Animal welfare: Should we change housing to better accommodate the animal or change the animal to accommodate the housing? CAB Review: Perspectives in Agriculture, Veterinary Science, Nutrition and Nature Resources. 2007;**2**:47-61

[206] Muir WM. Group selection for adaptation to multiple-hen cages: Selection program and direct responses. Poultry Science. 1996;**75**:447-458

[207] Cheng HW, Muir WM. Chronic social stress differentially regulates neuroendocrine responses in laying hens: II. Genetic basis of adrenal responses under three different social conditions. Psychoneuroendocrinology. 2004;**29**:961-971

[208] Cheng HW, Singleton P, Muir WM. Social stress in laying hens: Differential effect of genetic-environmental interactions on plasma dopamine concentrations and adrenal function in genetically selected chickens. Poultry Science. 2003;**82**:192-198

[209] Cicchetti D, Posner MI. Cognitive and affective neuroscience and developmental psychopathology. Development and Psychopathology. 2005;**17**:569-575

[210] Siever LJ. The neurobiology of aggression and violence. CNS Spectrums. 2015;**20**:254-279

[211] Dinan TG, Cryan JF. Mood by microbe: Towards clinical translation. Genome Medicine. 2016;**8**:36

[212] Hu JY, Chen H, Cheng HW. Effect of direct-fed microbials, *Bacillus subtilis*, on production performance,

serotonin concentrations and behavioral parameters in a selected dominant strain of White Leghorn hens. International Journal of Poultry Science. 2018;**17**:106-115

[213] Dennis RL, Cheng HW. The dopaminergic system and aggression in laying hens. Poultry Science. 2011;**90**:2440-2448

[214] D'Eath RB, Keeling LJ. Social discrimination and aggression by laying hens in large groups: From peck orders to social tolerance. Applied Animal Behaviour Science. 2003;**84**:197-212

[215] Rushen J. The peck orders of chickens—How do they develop and why are they linear. Animal Behaviour. 1982;**30**:1129-1137

[216] File SE. Factors controlling measures of anxiety and responses to novelty in the mouse. Behavioural Brain Research. 2001;**125**:151-157

[217] Fox AS, Kalin NH. A translational neuroscience approach to understanding the development of social anxiety disorder and its pathophysiology. The American Journal of Psychiatry. 2014;**171**:1162-1173

[218] Guhl AM. Psycho-physiological factors and social behavior related to sexual behavior in birds. Transactions of the Kansas Academy of Science. 1960;**63**:85-95

[219] Jager A, Maas DA, Fricke K, de Vries RB, Poelmans G, Glennon JC. Aggressive behavior in transgenic animal models: A systematic review. Neuroscience and Biobehavioral Reviews. 2018;**91**:198-217

[220] Koolhaas JM, Coppens CM, de Boer SF, Buwalda B, Meerlo P, Timmermans PJ. The resident-intruder paradigm: A standardized test for aggression, violence and social stress. Journal of Visualized Experiments. 2013;**77**:e4367

- [221] de Weerth C. Do bacteria shape our development? Crosstalk between intestinal microbiota and HPA axis. *Neuroscience and Biobehavioral Reviews*. 2017;**83**:458-471
- [222] Aslam H, Green J, Jacka FN, Collier F, Berk M, Pasco J, et al. Fermented foods, the gut and mental health: A mechanistic overview with implications for depression and anxiety. *Nutritional Neuroscience*. 2018;**11**:1-13
- [223] Cerdó T, García-Santos JA, G Bermúdez M, Campoy C. The role of probiotics and prebiotics in the prevention and treatment of obesity. *Nutrients*. 2019;**11**. pii: E635
- [224] Cuevas-Sierra A, Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Martinez JA. Diet, gut microbiota, and obesity: Links with host genetics and epigenetics and potential applications. *Advances in Nutrition*. 2019;**10**(suppl_1):S17-S30
- [225] Ma T, Suzuki Y, Guan LL. Dissect the mode of action of probiotics in affecting host-microbial interactions and immunity in food producing animals. *Veterinary Immunology and Immunopathology*. 2018;**205**:35-48
- [226] Roubalová R, Procházková P, Papežová H, Smitka K, Bilej M, Tlaskalová-Hogenová H. Anorexia nervosa: Gut microbiota-immune-brain interactions. *Clinical Nutrition*. 2019. <https://doi.org/10.1016/j.clnu.2019.03.023>
- [227] Abautret-Daly Á, Dempsey E, Parra-Blanco A, Medina C, Harkin A. Gut-brain actions underlying comorbid anxiety and depression associated with inflammatory bowel disease. *Acta Neuropsychiatrica*. 2018;**30**:275-296
- [228] Foster JA, Lyte M, Meyer E, Cryan JF. Gut microbiota and brain function: An evolving field in neuroscience. *The International Journal of Neuropsychopharmacology*. 2015;**19**:1-7
- [229] Lopes RCSO, Balbino KP, Jorge MP, Ribeiro AQ, Martino HSD, Alfenas RCG. Modulation of intestinal microbiota, control of nitrogen products and inflammation by pre/probiotics in chronic kidney disease: A systematic review. *Nutrición Hospitalaria*. 2018;**35**:722-730
- [230] Park C, Brietzke E, Rosenblat JD, Musial N, Zuckerman H, Ragguett RM, et al. Probiotics for the treatment of depressive symptoms: An anti-inflammatory mechanism? *Brain, Behavior, and Immunity*. 2018;**73**:115-124
- [231] Kane L, Kinzel J. The effects of probiotics on mood and emotion. *JAAPA: Official journal of the American Academy of Physician Assistants*. 2018;**31**:1-3
- [232] Pirbaglou M, Katz J, de Souza RJ, Stearns JC, Motamed M, Ritvo P. Probiotic supplementation can positively affect anxiety and depressive symptoms: A systematic review of randomized controlled trials. *Nutrition Research*. 2016;**36**:889-898
- [233] Reis DJ, Ilardi SS, Punt SEW. The anxiolytic effect of probiotics: A systematic review and meta-analysis of the clinical and preclinical literature. *PLoS One*. 2018;**13**:e0199041
- [234] Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic *Bifidobacterium infantis* in the maternal separation model of depression. *Neuroscience*. 2010;**170**:1179-1188
- [235] Sanders A, Rackers H, Kimmel M. A role for the microbiome in mother-infant interaction and perinatal depression. *International Review of Psychiatry*. 2019;**20**:1-15

- [236] Slykerman RF, Hood F, Wickens K, JMD T, Barthow C, Murphy R, et al. Effect of *Lactobacillus rhamnosus* HN001 in pregnancy on postpartum symptoms of depression and anxiety: A randomised double-blind placebo-controlled trial. *eBioMedicine*. 2017;**24**:159-165
- [237] Kantak PA, Bobrow DN, Nyby JG. Obsessive-compulsive-like behaviors in house mice are attenuated by a probiotic (*Lactobacillus rhamnosus* GG). *Behavioural Pharmacology*. 2014;**25**:71-79
- [238] Romijn AR, Rucklidge JJ. Systematic review of evidence to support the theory of psychobiotics. *Nutrition Reviews*. 2015;**73**:675-693
- [239] Gareau MG. Microbiota-gut-brain axis and cognitive function. *Advances in Experimental Medicine and Biology*. 2014;**817**:357-371
- [240] Mohajeri MH, La Fata G, Steinert RE, Weber P. Relationship between the gut microbiome and brain function. *Nutrition Reviews*. 2018;**76**:481-496
- [241] Solas M, Milagro FI, Ramírez MJ, Martínez JA. Inflammation and gut-brain axis link obesity to cognitive dysfunction: Plausible pharmacological interventions. *Current Opinion in Pharmacology*. 2017;**37**:87-92
- [242] Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: A systematic review. *Clinical Interventions in Aging*. 2018;**13**:1497-1511
- [243] Joseph JM, Law C. Cross-species examination of single- and multi-strain probiotic treatment effects on neuropsychiatric outcomes. *Neuroscience and Biobehavioral Reviews*. 2019;**99**:160-197
- [244] Elisashvili V, Kachlishvili E, Chikindas ML. Recent advances in the physiology of spore formation for bacillus probiotic production. *Probiotics and Antimicrobial Proteins*. 2018. <https://doi.org/10.1007/s12602-018-9492-x>
- [245] Cartman ST, La Ragione RM, Woodward MJ. *Bacillus subtilis* spores germinate in the chicken gastrointestinal tract. *Applied and Environmental Microbiology*. 2008;**74**:5254-5258
- [246] Mingmongkolchai S, Panbangred W. *Bacillus* probiotics: An alternative to antibiotics for livestock production. *Journal of Applied Microbiology*. 2018;**124**:1334-1346
- [247] Duc LH, Hong HA, Barbosa TM, Henriques AO, Cutting SM. Characterization of *Bacillus* probiotics available for human use. *Applied and Environmental Microbiology*. 2004;**70**:2161-2171
- [248] Hong HA, Huang JM, Khaneja R, Hiep LV, Urdaci MC, Cutting SM. The safety of *Bacillus subtilis* and *Bacillus indicus* as food probiotics. *Journal of Applied Microbiology*. 2008;**105**:510-520
- [249] Konuray G, Erginkaya Z. Potential use of *Bacillus coagulans* in the food industry. *Foods*. 2018;**7**. pii: E92
- [250] Grant A, Gay CG, Lillehoj HS. *Bacillus* spp. as direct-fed microbial antibiotic alternatives to enhance growth, immunity, and gut health in poultry. *Avian Pathology*. 2018;**47**:339-351
- [251] Latorre JD, Hernandez-Velasco X, Vicente JL, Wolfenden R, Hargis BM, Tellez G. Effects of the inclusion of a *Bacillus* direct-fed microbial on performance parameters, bone quality, recovered gut microflora, and intestinal morphology in broilers consuming a grower diet containing corn distillers dried grains with solubles. *Poultry Science*. 2017;**96**:2728-2735

- [252] Foligne B, Peys E, Vandenkerckhove J, Van Hemel J, Dewulf J, Breton J, et al. Spores from two distinct colony types of the strain *Bacillus subtilis* PB6 substantiate anti-inflammatory probiotic effects in mice. *Clinical Nutrition*. 2012;**31**:987-994
- [253] Okamoto K, Fujiya M, Nata T, Ueno N, Inaba Y, Ishikawa C, et al. Competence and sporulation factor derived from *Bacillus subtilis* improves epithelial cell injury in intestinal inflammation via immunomodulation and cytoprotection. *International Journal of Colorectal Disease*. 2012;**27**:1039-1046
- [254] Bernardeau M, Lehtinen MJ, Forssten SD, Nurminen P. Importance of the gastrointestinal life cycle of *Bacillus* for probiotic functionality. *Journal of Food Science and Technology*. 2017;**54**:2570-2584
- [255] Elshaghabee FMF, Rokana N, Gulhane RD, Sharma C, Panwar H. *Bacillus* as potential probiotics: Status, concerns, and future perspectives. *Frontiers in Microbiology*. 2017;**8**:1490
- [256] El Aidy S, Dinan TG, Cryan JF. Gut microbiota: The conductor in the orchestra of immune-neuroendocrine communication. *Clinical Therapeutics*. 2015;**37**:954-967
- [257] Duncan IJ. Behavior and behavioral needs. *Poultry Science*. 1998;**77**:1766-1772
- [258] Fraser D, Rushen J. Aggressive behavior. *The Veterinary Clinics of North America. Food Animal Practice*. 1987;**3**:285-305
- [259] Rodenburg TB, Tuytens FA, Sonck B, De Reu K, Herman L, Zoons J. Welfare, health, and hygiene of laying hens housed in furnished cages and in alternative housing systems. *Journal of Applied Animal Welfare Science*. 2005;**8**:211-226
- [260] Tablante NL, Vaillancourt JP, Martin SW, Shoukri M, Estevez I. Spatial distribution of cannibalism mortality in commercial laying hens. *Poultry Science*. 2000;**79**:705-708
- [261] Cheng HW. Morphopathological changes and pain in beak trimming laying hens. *World's Poultry Science Journal*. 2006;**62**:41-52
- [262] Hester PY. Impact of science and management on the welfare of egg laying strains of hens. *Poultry Science*. 2005;**84**:687-696
- [263] Kriegseis I, Bessei W, Meyer B, Zentek J, Würbel H, Harlander-Matauschek A. Feather-pecking response of laying hens to feather and cellulose-based rations fed during rearing. *Poultry Science*. 2012;**91**:1514-1521
- [264] van Krimpen MM, Kwakkel RP, van der Peet-Schwering CM, den Hartog LA, Verstegen MW. Effects of nutrient dilution and nonstarch polysaccharide concentration in rearing and laying diets on eating behavior and feather damage of rearing and laying hens. *Poultry Science*. 2009;**88**:759-773
- [265] van Krimpen M. Feeding to prevent feather pecking in layers. *World Poultry*. 2012. Available from: <http://www.worldpoultry.net/Layers/Nutrition/2012/5/Feeding-to-prevent-feather-pecking-in-layers-WP010372W/> [Accessed: October 2018]
- [266] Blokhuis HJ, van der Haar JW. Effects of pecking incentives during rearing on feather pecking of laying hens. *British Poultry Science*. 1992;**33**:17-24
- [267] Kalmendal R, Bessei W. The preference for high-fiber feed in laying hens divergently selected on

feather pecking. Poultry Science. 2012;**91**:1785-1789

[268] Lambton SL, Nicol CJ, Friel M, Main DC, McKinstry JL, Sherwin CM, et al. A bespoke management package can reduce levels of injurious pecking in loose-housed laying hen flocks. The Veterinary Record. 2013;**172**:423

[269] Appleby MC. Modification of laying hen cages to improve behavior. Poultry Science. 1998;**77**:1828-1832

[270] Hartcher KM, Tran KT, Wilkinson SJ, Hemsworth PH, Thomson PC, Cronin GM. The effects of environmental enrichment and beak-trimming during the rearing period on subsequent feather damage due to feather-pecking in laying hens. Poultry Science. 2015;**94**:852-859

[271] Bolhuis JE, Ellen ED, Van Reenen CG, De Groot J, Ten Napel J, Koopmanschap RE, et al. Effects of genetic group selection against mortality on behavior and peripheral serotonin in domestic laying hens with trimmed and intact beaks. Physiology & Behavior. 2009;**97**:470-475

[272] Hercigonja Novkovic V, Rudan V, Pivac N, Nedic G, Muck-Seler D. Platelet serotonin concentration in children with attention-deficit/hyperactivity disorder. Neuropsychobiology. 2009;**59**:17-22

[273] Rosado B, Garcia-Belenguer S, Palacio J, Chacon G, Villegas A, Alcalde AI. Serotonin transporter activity in platelets and canine aggression. Veterinary Journal. 2010;**186**:104-105

[274] Mann JJ, Brent DA, Arango V. The neurobiology and genetics of suicide and attempted suicide: A focus on the serotonergic system. Neuropsychopharmacology. 2001;**24**:467-477

[275] McDonald MD, Gonzalez A, Sloman KA. Higher levels of

aggression are observed in socially dominant toadfish treated with the selective serotonin reuptake inhibitor, fluoxetine. Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology. 2011;**153**:107-112

[276] Darbaky Y, Evrard B, Patrier S, Falenta J, Garcin S, Tridon A, et al. Oral probiotic treatment of *Lactobacillus rhamnosus* Lcr35(R) prevents visceral hypersensitivity to a colonic inflammation and an acute psychological stress. Journal of Applied Microbiology. 2016;**122**:188-200

[277] Giannetti E, Staiano A. Probiotics for irritable Bowel syndrome: Clinical data in children. Journal of Pediatric Gastroenterology and Nutrition. 2016;**63**:S25-S26

[278] Lacy BE, Chey WD, Lembo AJ. New and emerging treatment options for irritable Bowel syndrome. Gastroenterol Hepatol (N Y). 2015;**11** (4 Suppl 2):1-19

[279] Liang S, Wang T, Hu X, Luo J, Li W, Wu X, et al. Administration of *lactobacillus helveticus* Ns8 improves behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress. Neuroscience. 2015;**310**:561-577

[280] Cremon C, Carini G, Wang B, Vasina V, Cogliandro RF, De Giorgio R, et al. Intestinal serotonin release, sensory neuron activation, and abdominal pain in irritable bowel syndrome. The American Journal of Gastroenterology. 2011;**106**:1290-1298

[281] Kanauchi O, Mitsuyama K, Komiyama Y, Yagi M, Andoh A, Sata M. Preventive effects of enzyme-treated rice fiber in a restraint stress-induced irritable bowel syndrome model. International Journal of Molecular Medicine. 2010;**25**:547-555

- [282] Gershon MD. Review article: Serotonin receptors and transporters—Roles in normal and abnormal gastrointestinal motility. *Alimentary Pharmacology & Therapeutics* (Suppl). 2004;**7**:3-14
- [283] Tack J, Vanuytsel T, Corsetti M. Modern management of irritable Bowel syndrome: More than motility. *Digestive Diseases*. 2016;**34**:566-573
- [284] Wikoff WR, Anfora AT, Liu J, Schultz PG, Lesley SA, Peters EC, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proceedings of the National Academy of Sciences of the United States of America*. 2009;**106**:3698-3703
- [285] Bravo JA, Julio-Pieper M, Forsythe P, Kunze W, Dinan TG, Bienenstock J, et al. Communication between gastrointestinal bacteria and the nervous system. *Current Opinion in Pharmacology*. 2012;**12**:667-672
- [286] Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterology and Motility*. 2011;**23**:255-264
- [287] Bercik P, Denou E, Collins J, Jackson W, Lu J, Jury J, et al. The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. *Gastroenterology*. 2011;**141**:599-609.e3
- [288] Pietraszek MH, Takada Y, Yan D, Urano T, Serizawa K, Takada A. Relationship between serotonergic measures in periphery and the brain of mouse. *Life Sciences*. 1992;**51**:75-82
- [289] Sarrias MJ, Martínez E, Celada P, Udina C, Alvarez E, Artigas F. Plasma free 5HT and platelet 5HT in depression: Case-control studies and the effect of antidepressant therapy. *Advances in Experimental Medicine and Biology*. 1991;**294**:653-658
- [290] Guslandi M. Probiotic agents in the treatment of irritable bowel syndrome. *The Journal of International Medical Research*. 2007;**35**:583-589
- [291] Yan FF, Wang WC, Cheng HW. *Bacillus subtilis* based probiotic improved bone mass and altered brain serotonergic and dopaminergic systems in broiler chickens. *Journal of Functional Foods*. 2018;**49**:501-509
- [292] Forsythe P, Sudo N, Dinan T, Taylor VH, Bienenstock J. Mood and gut feelings. *Brain, Behavior, and Immunity*. 2010;**24**:9-16
- [293] Bienenstock J, Kunze W, Forsythe P. Microbiota and the gut-brain axis. *Nutrition Reviews*. 2015;**73**:28-31
- [294] Di Meo F, Donato S, Di Pardo A, Maglione V, Filosa S, Crispi S. New therapeutic drugs from bioactive natural molecules: The role of gut microbiota metabolism in neurodegenerative diseases. *Current Drug Metabolism*. 2018;**19**:478-489
- [295] Kuo PH, Chung YE. Moody microbiome: Challenges and chances. *Journal of the Formosan Medical Association*. 2019;**118**(Suppl 1):S42-S54
- [296] Liang S, Wu X, Jin F. Gut-brain psychology: Rethinking psychology from the microbiota-gut-brain axis. *Frontiers in Integrative Neuroscience*. 2018;**12**:33
- [297] Roy Sarkar S, Banerjee S. Gut microbiota in neurodegenerative disorders. *Journal of Neuroimmunology*. 2019;**328**:98-104
- [298] Campion D, Ponzo P, Alessandria C, Saracco GM, Balzola F. The role of microbiota in autism spectrum disorders. *Minerva Gastroenterologica e Dietologica*. 2018;**64**:333-350
- [299] Cekici H, Sanlier N. Current nutritional approaches in managing

autism spectrum disorder: A review. *Nutritional Neuroscience*. 2019;**22**(3):145-155

[300] Martin CR, Mayer EA. Gut-brain axis and behavior. Nestlé Nutrition Institute Workshop Series. 2017;**88**:45-53

[301] Tabouy L, Getselter D, Ziv O, Karpuy M, Tabouy T, Lukic I, et al. Dysbiosis of microbiome and probiotic treatment in a genetic model of autism spectrum disorders. *Brain, Behavior, and Immunity*. 2018;**73**:310-319

[302] Luk B, Veeraragavan S, Engevik M, Balderas M, Major A, Runge J, et al. Postnatal colonization with human "infant-type" bifidobacterium species alters behavior of adult gnotobiotic mice. *PLoS One*. 2018;**13**:e0196510

[303] Matthews DM, Jenks SM. Ingestion of *Mycobacterium vaccae* decreases anxiety-related behavior and improves learning in mice. *Behavioural Processes*. 2013;**96**:27-35

[304] Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*. 2013;**155**:1451-1463

[305] Salvatore S, Pensabene L, Borrelli O, Saps M, Thapar N, Concolino D, et al. Mind the gut: Probiotics in paediatric neurogastroenterology. *Beneficial Microbes*. 2018;**10**:1-16

[306] Cengiz O, Koksai BH, Tath O, Sevim O, Ahsan U, Uner AG, et al. Effect of dietary probiotic and high stocking density on the performance, carcass yield, gut microflora, and stress indicators of broilers. *Poultry Science*. 2015;**94**:2395-2403

[307] Liao XD, Ma G, Cai J, Fu Y, Yan XY, Wei XB, et al. Effects of *Clostridium butyricum* on growth performance,

antioxidation, and immune function of broilers. *Poultry Science*. 2015;**94**:662-667

[308] Grimes JL, Rahimi S, Oviedo E, Sheldon BW, Santos FB. Effects of a direct-fed microbial (Primalac) on turkey poult performance and susceptibility to oral *Salmonella* challenge. *Poultry Science*. 2008;**87**:1464-1470

[309] Davis ME, Parrott T, Brown DC, de Rodas BZ, Johnson ZB, Maxwell CV, et al. Effect of a *Bacillus*-based direct-fed microbial feed supplement on growth performance and pen cleaning characteristics of growing-finishing pigs. *Journal of Animal Science*. 2008;**86**:1459-1467

[310] Yoruk MA, Gul M, Hayirli A, Macit M. The effects of supplementation of humate and probiotic on egg production and quality parameters during the late laying period in hens. *Poultry Science*. 2004;**83**:84-88

[311] Lee DK, Park JE, Kim MJ, Seo JG, Lee JH, Ha NJ. Probiotic bacteria, *B. longum* and *L. acidophilus* inhibit infection by rotavirus in vitro and decrease the duration of diarrhea in pediatric patients. *Clinics and Research in Hepatology and Gastroenterology*. 2015;**39**:237-244

[312] Lee KW, Lee SH, Lillehoj HS, Li GX, Jang SI, Babu US, et al. Effects of direct-fed microbials on growth performance, gut morphometry, and immune characteristics in broiler chickens. *Poultry Science*. 2010;**89**:203-216

[313] Sen S, Ingale SL, Kim YW, Kim JS, Kim KH, Lohakare JD, et al. Effect of supplementation of *Bacillus subtilis* LS 1-2 to broiler diets on growth performance, nutrient retention, caecal microbiology and small intestinal morphology. *Research in Veterinary Science*. 2012;**93**:264-268