Chapter

Gestational Tryptophan Fluctuation Underlying Ontogenetic Origin of Neuropsychiatric Disorders

Xiaohong Huang, Xiaohua Li and Heng-Wei Cheng

Abstract

Neuropsychiatry underlies personality development and social functioning. Borderline personality disorder exhibits high trait aggression and is associated with tryptophan hydroxylase polymorphisms. The acute tryptophan depletion reduces plasma and cerebrospinal fluid tryptophan availability and brain serotonin concentrations, leading to alterations in personality and trait-related behaviors. Tryptophan is essential for fatal neurodevelopment and immunomodulation in pregnancy. Gestational tryptophan fluctuation induced by maternal metabolic disorders or drug administrations may account for the maternal-fetal transmission determining neurogenesis and microbial development, consequentially shaping the long-standing patterns of thinking and behavior. However, it is not possible to assess the gestational tryptophan exposure effects on fetal brain and gastrointestinal system in humans for ethical reasons. The maternal–fetal microbe transmission in rodents during gestation, vaginal delivery, and breastfeeding is inevitable. Chicken embryo may be an alternative and evidence from the chicken embryo model reveals that gestational tryptophan fluctuation, i.e., exposed to excessive tryptophan or its metabolite, serotonin, attenuates aggressiveness and affects peer sociometric status. This chapter discusses the gestational tryptophan fluctuation as a risk factor of personality disorders in offspring and the prevention of personality disorders by dietary tryptophan control and medication therapy management during pregnancy.

Keywords: gestation, tryptophan, neuropsychiatry, neuroendocrine, microbiota-gut-brain axis

1. Introduction

Personality is mediated by multi-factors, including brain chemistry and life experiences, reflecting people's long-standing patterns of thinking and behavior [1]. Strong association between childhood adversity and a diagnosis of personality disorder in young adulthood has been revealed by a cohort study in 2017 among

individuals born in Stockholm County [2]. Indeed, personality already starts in the womb, and prenatal experience influences temperament development [3]. A longitudinal birth cohort study in 2019 revealed the potential association between prenatal stress exposure and personality disorders in Finland [4]. However, scientifically plausible inferences regarding the causality are not assessable in view of those retrospective data. In the context that the evidence from prospective longitudinal studies supports early-life experience programming personality development, it is crucial to investigate how early-life stimuli cause personality disorders and relevant neurobiological mechanisms.

Borderline personality disorder (BPD, ICD-10-CM code F60.3) patients present high trait aggression [5], and BPD is associated with the polymorphism of tryptophan hydroxylase (TPH) 1 and TPH2 [6–8]. Tryptophan (Trp) is essential for fetal growth including neurodevelopment and immunomodulation in pregnancy [9]. Gestational Trp fluctuation caused by maternal metabolic disorders or drug administrations may account for the maternal-fetal transmission determining neurogenesis and microbial development, consequentially shaping the long-standing patterns of thinking and behavior in offspring [10–12]. Several current studies indicate that gestational Trp exposure yields bullying victim while exposed to excessive serotonin (5-hydroxytryptophan, 5-HT) reduces aggressiveness in bullies [11, 12]. Such studies improve our understanding of temperament development and hold the promise to promote advances in the preventing and treating personality disorders.

2. Ontogenetic origin of neuropsychiatric disorders

2.1 Neuropsychiatric basis of personality disorders

Personality has been broadly considered in neuropsychiatry and vice versa [13]. People with personality disorders have more rigid thinking and hyperreactive behaviors, which makes it hard for them to perceive and adapt to the surrounding situations and people. Patients with BPD display increased stress vulnerability, which is linked to the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis [14], with lower baseline cortisol levels compared with healthy controls [15]. The cortisol awakening response, presumed to mirror maladaptive neuroendocrine processes, is increased in female individuals with BPD [14]. Moreover, the role of cortisol and testosterone in regulating aggressive and socially dominant behavior in children and adults has been proposed by the dual-hormone hypothesis [16], suggesting the involvement of the hypothalamic-pituitary-gonadal (HPG) axis also. The first evidence from mixed-sex community adolescents reveals that the joint effects of testosterone and cortisol on externalizing problems, which is especially pronounced in individuals with disagreeableness and emotional instability personality pathology traits [16]. Hence, the development and activity of the neuroendocrine system lay the foundation of personality traits. And, the link between personality traits and neurodevelopmental disorders (NDDs) has been explored by Child and Adolescent Twin Study in Sweden (CATSS), such as attention deficit hyperactivity disorder (ADHD, ICD-10 codes F90) and autism spectrum disorder (ASD, ICD-10 code F84.0) [13]. The character dimensions of cooperativeness and self-directedness and ASD are negatively correlated and ADHD alike [13].

2.2 Maternal-fetal transmission in ontogenetic origin of neuropsychiatric disorders

Barker's hypothesis proposes the ontogenetic origin of adult diseases [17]. Maternal malnutrition or drug administration altering maternal metabolism influences fetal development through maternal-fetal transmission. The correlation between maternal 5-HT levels and offspring cognitive ability has been identified in ASD [18]. A nationwide cohort study in France found that increased NDDs occurrence is associated with gestational exposure to valproate, an antiepileptic drug [19]. Moreover, antenatal valproate exposure induces changes and abnormalities in the gastrointestinal microstructure and function in rats, indicated by the thinned tunica mucosa and tunica muscularis of the ileum [20]. The changes parallel the gastrointestinal symptoms in ASD patients [20]. Moreover, patients with ASD have significant changes in the gut microbiome, e.g., increased abundance of family *Sutterellaceae* and *Enterobacteriaceae* and decreased abundance of genus *Bifidobacterium* [21]. Hence, maternal metabolic fluctuation may directly interfere fetal neurogenesis and/or indirectly reprogram gut microbial development to alter the function of the microbiota-gut-brain (MGB) axis with the potential for neuropsychiatric disorders in offspring.

3. Tryptophan in pregnancy

Tryptophan, an essential amino acid, is critical for pregnancy attributing to fetal neurogenesis and immunomodulation [9]. Tryptophan is the sole precursor of 5-HT [22]. Maternal circuiting Trp takes part in fetal brain development via the 5-HT pathway regulating synaptogenesis and neuronal maturation, e.g., the thalamocortical pathfinding is disrupted by modifying the 5-HT abundance in the embryonic mouse brain [23]. Tryptophan is synthesized into 5-HT in the placenta and delivered to the fetal brain or delivered directly to the fetal brain, then synthesized into 5-HT [22]. Two BPD risk factors, i.e., the 5-HT 1A receptor promoter polymorphism (rs6295) and dopamine (DA) transporter repeat allele, have been identified in 367 patients with major depressive disorders (MDDs) [24]. Another metabolic pathway of placental Trp is degradation along the cytokine-induced activated Trp catabolite (TRYCAT) pathway, producing kynurenines (KYNs) to suppress T cell responses [25]. A disturbed TRYCAT pathway in the fetal brain has been characterized in people with schizophrenia (ICD-10 code F20.9), a neurodevelopmental disorder [26]. Low plasma concentrations of Trp and KYN have been found in patients with severe anxiety and depression during pregnancy [27] while excess Trp causes preeclampsia (ICD-10-CM code O14.90), which results in long-term endocrine morbidity in offspring [28]. Preeclampsia has been associated with increased NDDs occurrence, including ASD, ADHD, mental retardation (ICD-10 code F70–F79), epilepsy (ICD-10 code G40) [29]. Both the increases in maternal urinary Trp concentration and ASD risk of offspring have been seen in gestational diabetes mellitus (ICD-10-CM code O24.419) patients [30, 31]. Moreover, antenatal stress adversely affects neurodevelopment via disrupting placental Trp metabolism, laying the neurobiological foundation of psychiatric disorders [32]. The gut Trp-metabolizing microbes, i.e., the genera *Parasutterella* and *Bifidobacterium*, are reduced in the dam and offspring following prenatal maternal stress [33]. Thus, malnutrition and drug administrations during pregnancy may have altered placental Trp availability, the function of TRYCAT pathway, and/or the abundance of gut Trp-metabolizing microbes, leading to neuropsychiatric disorders in offspring.

4. Tryptophan and personality traits

4.1 Tryptophan hydroxylase polymorphisms in personality traits and disorders

Tryptophan hydroxylases (TPHs), the rate-limiting enzymes, convert Trp into 5-HT at the different locations, i.e., TPH1 in the body and TPH2 in the brain [22]. The polymorphisms within TPH genes, involved in regulating the Trp–5-HT conversion, are relevant to personality traits and disorders. The relationship between TPH single-nucleotide polymorphisms (SNPs) and personality traits/disorders has been reviewed in **Table 1**. For example, rs1800532 is associated with trait emotional intelligence [34], anger-related traits [35, 36], antisocial personality disorder [39], and BPD [6]. However, negative results have been reported in other studies [37, 38]. The controversy may be caused by the sampling population or sample size. And, it may be resolved by the involvement of other SNPs, i.e., haplotype [7, 8]. For example, a TPH2 "risk" haplotype (rs2171363, rs6582078, rs1352250) has been identified in a well-characterized clinical sample of 251 patients with personality disorders and 103 healthy controls, associated with BPD diagnosis, affective lability, and aggression [8].

Gene	Sample	Single nucleotide polymorphism	Personality trait/ disorder	Ref.
TPH1	336 healthy Korean college students	rs1800532	Trait emotional intelligence	[34]
	251 community-derived volunteers in Pittsburgh	rs1800532	Anger-related traits and aggression	[35]
	544 suicide attempters in Switzerland	rs1800532	Anger-related traits	[36]
	345 Japanese healthy subjects	rs1800532	Not associated with personality traits	[37]
	228 healthy Korean women	rs1800532	Not associated with anger-related traits	[38]
	310 participants with antisocial personality disorder and 200 with no antisocial personality disorder	rs1800532	Antisocial personality disorder	[39]
	100 patients diagnosed with borderline personality disorder and 101 non-psychiatric controls	rs1800532	Borderline personality disorder	[6]
	86 suicide attempters and 154 community-based healthy volunteers in German	rs1800532, rs1799913	Anger-related traits	[40]
	Caucasian students of German ancestry without any history of psychopathology or drug abuse: 108 smokers and 144 nonsmokers	rs1799913	Neurotic aggression	[41]
	253 healthy Japanese subjects	rs1799913	Not associated with personality traits	[42]
	95 Caucasian women with borderline personality disorder had attempted suicide at least twice during their lifetime and 98 women without psychiatric history	rs4537731, rs684302, rs211105, rs1800532, rs1799913, rs7933505	Borderline personality disorder	[7]

Gene	Sample	Single nucleotide polymorphism	Personality trait/ disorder	Ref.
TPH2	1176 Estonian subjects	rs4570625	Adaptive impulsivity and trait anxiety	[43]
	228 healthy Korean women	rs4570625	Anger-related traits	[38]
	1576 Estonian teenagers	rs4570625	Neuroticism and conscientiousness	[44]
	63 healthy Korean women	rs4570625	Anger-related traits	[45]
	336 healthy volunteers of German descent	rs4570625	Anxiety-related traits	[46]
	251 patients with personality disorders and 103 healthy controls	rs2171363, rs6582078, rs1352250	Borderline personality disorder and aggression	[8]

Table 1.
Non-comprehensive review of the relationship between tryptophan hydroxylase polymorphisms and personality traits/disorders in humans.

4.2 Tryptophan in personality traits and disorders

The existing evidence regarding Trp interacting with personality and regulating trait-related behaviors has been reviewed and presented in **Table 2**. The acute tryptophan depletion (ATD) method has been developed to reduce plasma and

Factor	Sample	Intervention	Effects on personality traits/ disorders	Ref.
Tryptophan condition	52 male and female students	Acute Tryptophan Depletion (Young)	• Neuroticism discrimination is weakened	[47]
	16 healthy males	Acute Tryptophan Depletion (Young)	• Discounting rates are increased in nine participants but are unchanged or decreased in seven participants • Participants with increased discounting rate have higher neuroticism and lower self-directedness	[48]
	28 healthy males	Tryptophan enhancement/ depletion	• Trait hostility and prolactin responses to tryptophan manipulation are negatively correlated following enhancement and positively following depletion	[49]
	20 males with attention deficit hyperactivity disorder	Acute tryptophan depletion (Moja-De)	• Rates of reactive aggression in males with attention deficit hyperactivity disorder are decreased after low provocation	[50]
	20 healthy males		• Rates of reactive aggression in healthy males are increased after low provocation	

Factor	Sample	Intervention	Effects on personality traits/ disorders	Ref.
Tryptophan condition × Trait	39 healthy males and 34 healthy females	Acute Tryptophan Depletion (Young)	• Guilt is preferentially elevated in highly empathic participants • Annoyance is potentiated in participants high in trait psychopathy	[51]
	24 high and 24 low trait aggression healthy males	Tryptophan enhancement/ depletion	• In aggressive traits, subjective and objective aggression is increased by tryptophan depletion and decreased by tryptophan enhancement • Change in a low aggressive group is absent	[52]
	13 young adults with and 12 without family history of mood disorder	Acute Tryptophan Depletion (Young)	• Abnormalities in emotional processing are detected in the individuals with no personal psychiatric history but at high familial risk for depression	[53]
	22 male adolescents with attention deficit hyperactivity disorder	Acute tryptophan depletion (Moja-De)	• Aggressive behavior is increased in low-grade impulsive patients • Aggressive behavior is not affected in high-grade impulsive patients	[54]
	6 healthy subjects with high trait hostility and aggression and 6 with low	Acute tryptophan depletion (Moja-De)	• A rapid mood-lowering effect is detected on trait aggression healthy women • No change is detected in high-aggressive men and low-aggressive women and men	[55]
	34 low-hostile and 33 high-hostile individuals	Dietary tryptophan enhancement	• More negative mood and higher craving for alcohol are found in high-hostile individuals • Subjective or physiological effects are not detected • Stress-induced increase in craving is facilitated in high-hostile individuals by dietary tryptophan enhancement	[56]

Table 2.
Non-comprehensive review of the effects of tryptophan on personality traits and disorders in humans.

cerebrospinal fluid Trp availability and central 5-HT concentrations, leading to alterations in personality and trait-related behaviors. Acute tryptophan depletion is firstly applied in humans by Concu et al. in 1977 [57]. And, the method has been modified

by researchers, including Moja [58] and Young [59]. For example, the compositions of the amino acid mixtures are distinct [58, 59]. And, the gender difference is taken into account, i.e., the amino acid quantities of both ATD and placebo balanced beverages differ between males and females [47]. Moreover, inconsistencies exist regarding the effects of ATD on personality traits and disorders, attributing to the health state and characteristics of the subjects. For instance, ATD increases the rates of reactive aggression in healthy males, while it has opposite effect on males with ADHD [50]. Moreover, the trait property makes a difference. Guilt is preferentially elevated in highly empathic participants following ATD intervention, while annoyance is potentiated in participants high in trait psychopathy [51]. Hence, maternal plasma (MP) Trp fluctuation underlies the psychopathology of personality disorders, which may interfere fetal personality development via the maternal–fetal transmission, especially in the premise that personality already starts in the womb [3].

5. Maternal tryptophan fluctuation alters neuroendocrine and microbial development in offspring

Maternal Trp fluctuation induced by Trp-enriched or -depleted diets during pregnancy alters fetal neurogenesis and microbial constitution, which may reprogram the development and activity of the MGB, HPA, and HPG axes in offspring. The existing evidence has been reviewed and presented in **Table 3**.

The table is adjusted based on [10].

5.1 Maternal tryptophan fluctuation alters behavioral exhibition via reprogramming the neuroendocrine system in offspring

Maternal Trp fluctuation has altered the development and activity of the HPA axis in offspring indicated by the decreased plasma corticosterone (CORT) concentrations post restraint stress in the female adolescent mice experienced Trp-deficiency during the embryogenesis [73]. Low endogenous cortisol levels are associated with potentially pathological, intrusive, emotional memory processing [74, 75]. More specifically, the low posttraumatic urinary cortisol levels have been identified as a risk factor of posttraumatic stress disorder (PTSD) [74]. Moreover, maternal Trp administration in mice alters the development and function of the HPG axis during offspring's pubertal maturation via regulating the productions of prolactin (PRL) and luteinizing hormone (LH) in the pituitary gland [63, 65, 66]. Trp-free diets from gestation to puberty cause hypoandrogenism and hypoprolactinemia in the male progeny [65, 66], while maternal administration of Trp-enriched diets increases serum LH in offspring at postnatal (P) 70 days [63]. Increased serum PRL is associated with a diagnosis of BPD [76], and hyperprolactinemia has been observed in people with neurotic and personality disorders [77]. Moreover, a high serum PRL level is associated with psychological stress responses in humans [78]. An acute psychosocial stressor increases testosterone in both BPD patients and healthy participants [79].

5.2 Maternal tryptophan fluctuation alters behavioral exhibition via reprogramming the gut microbiota in offspring

Multi-hits early-life stress alters gut microbiome and brain gene expression, laying the foundation of mental health in postnatal life [80, 81]. The gut microbiota works

Species	Treated Time	Control	Treatment	Exhibitions in offspring	Ref
Wistar rat	14 days prior to mating–P4mo*	Standard chow powder (3.5 g tryptophan/kg)	10 g tryptophan mixed with the diet (13.5 g tryptophan/kg)	• Decreased body weight of the male offspring at P4mo • Decreased serotonin concentration, tryptophan hydroxylase 2 activity, and serotonin uptake in the frontal cortex and brain stem	[60]
Hypertensive rat	7 continued days prior to mating	Stock chow diet	30 mg ryptophan /kg/day mixed with the diet	• Increased body weight and blood pressure during P5wk–P15wk • Increased brain weight at P20wk • Increased total serotonin metabolite content in the medulla at P20wk	[61]
Sprague-Dawley rat	E17	Saline vehicle	200 mg tryptophan /kg oral gavage	• Increased tryptophan, serotonin, and 5-hydroxyindoleacetic acid concentrations in the fetal brain at E17 and E18	[62]
Sprague-Dawley rat	E15–E21	Saline vehicle	200 mg tryptophan/kg oral gavage	• Increased serum prolactin at P40d and P70d • Increased serum luteinizing hormone at P70d • Increased forebrain serotonin and 5-hydroxyindoleacetic acid at P70d	[63]
Wistar rat	E19 and E21	0.1 N-HCl vehicle	250 mg tryptophan /kg intraperitoneal	• Increased intracerebral concentrations of Trp at E19 • Decreased valine, methionine, leucine, tyrosine, phenylalanine, and histidine at E19 • Increased phosphoserine, threonine, serine, glutamic acid, and tryptophan at E21 • Decreased methionine, leucine, and histidine at E21 • Increased protein synthesis activity indicated by [^{3}H] Leucine incorporation at E19 and E21	[64]
Sprague-Dawley rat	E14.5–late puberty	Control chow (0.22% tryptophan)	Tryptophan free diet (0.00% tryptophan)	• Dwarfism pups • Decreased serum growth hormone concentration in male and female offspring • Severe hypoprolactinemia • Normal right-timed onset of puberty in both male and female rats	[65, 66]

Species	Treated Time	Control	Treatment	Exhibitions in offspring	Ref
Wistar rat	E5–E21	Regular chow diet	Tryptophan-free diet (0.2% tryptophan)	• Unchanged brain weights in newborn pups • Decreased body weight in newborn pups • Reduced numbers of serotoninergic neurons at the dorsal raphe, especially at the medial and caudal sections of dorsal raphe, which contains the majority of serotoninergic neurons • Unchanged brain serotonin concentration	[67]
Sprague-Dawley rat	E1–E21	Control	200 mg tryptophan/kg oral gavage	• Increased kidney weight-to-body weight ratio at P12wk • Increase blood pressure in male offspring at P4wk, P6wk, P8wk, P10wk, and P12wk • Decreased plasma level of L-citrulline (a precursor of L-arginine) and symmetric dimethylarginine (an indirect inhibitor of NO synthase) • Increased mRNA expressions in the genes of aryl hydrocarbon receptor pathway	[68]
Chronic kidney disease Sprague-Dawley rat	E1–early postnatal life*			• Decreased systolic blood pressure, mean arterial pressure, and creatinine at P12wk • Decreased plasma level of L-citrulline and symmetric dimethylarginine • Altered the abundance of the tryptophan-metabolizing microbes, i.e., increased abundance of genus *Intestinimonas* and decreased abundance of genus *Turicibacter*	
Sprague-Dawley rat	E1–late puberty	Control chow (0.22% tryptophan)	Tryptophan free diet (0.00% tryptophan)	• Pronounced dwarfism pups • Decreased serum growth hormone concentration in males and females • Marked hypoandrogenism and severe hypoprolactinemia in males • Hypoprolactinemia in females • Right-timed pubertal maturation in both sexes	[65, 66]

Species	Treated Time	Control	Treatment	Exhibitions in offspring	Ref
Sprague-Dawley rat	E1–P12wk*	Control rat chow (0.22 g tryptophan p/100 g of pellets)	High- tryptophan diet (1 g tryptophan/100100 g of pellets)	• Increased blood serotonin, i.e., hyperserotonemia during P1wk–P12wk • Decreased blood growth hormone • Decreased activity of tryptophan hydroxylase1 in gastrointestinal tracts • Decreased insulin-like growth factor-I expression in hepatic and muscle tissues	[69]
Sprague-Dawley rat	E1–weaning	500 mg tryptophan /100 g diet	75 mg tryptophan/100 g diet	• Decreased average body weight at weaning • Unaffected opacities at P22d	[70]
Sprague-Dawley rat	E1–P25d *	TD.99366 control diet (1.8 g tryptophan /kg)	TD.08125 tryptophan-deficient diet (1 g tryptophan /kg)	• Normal body weight at P5d but reduced body weight at P15d and P25d • Decreased body temperatures at P15d and P25d • Unaffected oxygen consumption (V_{O2}) • Altered breathing pattern and decreased heart rates at P15d • Decreased ventilation (V_E) and V_E-to-V_{O2} ratios in both air and 7% CO_2 at P25d • Increased ventilatory response to CO_2 in male offspring at P5d and reduced at P15d and P25d in male and female offspring • Reduced medullary serotonin concentration, while similar serotoninergic neuronal number	[71]
Pig	Third trimester of gestation–delivery	2× tryptophan diet (0.26% tryptophan fed in the morning and afternoon)	High-low tryptophan diet (0.39% tryptophanfed in the morning and 0.13% tryptophan fed in the afternoon)	• Decreased birth healthy pig rate and birth weight of piglet per pen with similar total birth weight per pen • Decreased serum phosphoserine, taurine, cysteine, proline in newborns and increased liver *n*-6:*n*-3 polyunsaturated fat ratio • Altered gene expressions, including the genes related to cytotoxic effector regulation, nicotinamide adenine dinucleotide oxidation, reactive oxygen species metabolism, and tissue development	[72]

Species	Treated Time	Control	Treatment	Exhibitions in offspring	Ref
Outbred CD-1 mouse	Lactation (P0d–P8d)	Standard laboratory diet (0.14% tryptophan)	Tryptophan-deficient diet (0.00% tryptophan)	• Unchanged time spent in open sectors in the 0-maze test in adolescent daughters (P189d–P193d) • Unchanged time spent in floating in the forced-swim test in adolescent daughters • Unchanged time spent in the novel compartment in the novelty-seeking test in adolescent daughters • Unchanged achieved breakpoint in the progressive ratio operant procedure in adolescent daughters • Decreased plasma corticosterone concentrations and similar brain-derived neurotrophic factor concentrations following restraint stress in adolescent daughters	[73]

**The pups are fed the same diet as mothers throughout postnatal (P) life.*

Table 3.
Non-comprehensive review of the effects of maternal tryptophan administration on offspring behavioral and physiological exhibitions in experimental animals.

as a virtual endocrine organ [82]. It has been demonstrated in the chronic kidney disease (CKD) rats that gestational Trp prevents hypertension via reprograming the Trp-metabolic microbiome in offspring, increasing the abundance of genus *Intestinimonas* and decreasing the abundance of genus *Turicibacter* [68]. The abundance of *Turicibacter* is negatively associated with sociability traits [83]. Moreover, gut microbes regulate stress responses, i.e., the activity of the HPA axis, via the MGB axis. A decreased abundance of *Lactobacillus* has been associated with increased stress reactivity in the infant rhesus monkeys that experienced maternal separation [84].

5.3 The accompanied physiological alterations are associated with the neuropsychological impairment in offspring

The physiological alterations in the offspring following the maternal Trp administration, such as the changes in body weight (BW), blood pressure, and breath movement [60, 61, 65–68, 70–72, 85], may be underlying the altered neuroendocrine and gut microbial development. For example, host's eating behavior is manipulated by the gut microbes and neuroendocrine cells [86], which determines the growth of BW. The National Collaborative Perinatal Project (NCPP, New England) revealed a relationship between obstetrical complications and neuropsychological deficits in children aged 7 [87]. The dissatisfaction with body image followed by improper Trp administrations may have counterbalanced mental health, causing negative influences on the psychosocial development in offspring.

6. Inconsistency and barriers

6.1 Inconsistency in maternal tryptophan programming offspring neuropsychiatric development

This is not surprising that the outcomes of prenatal Trp exposure are of complex phenotypes, due to a sequential series of events during embryogenesis. Taking as an example the central nervous system (CNS), a sensitive target for gestational Trp exposure experiences vast majority of differentiation at cellular and nucleus levels. A small or subtle alteration in brain structure during fetal development can be progressively magnified over time and moderated by postnatal conditions, affecting emotional regulation and decision-making [88]. Issues are likely to cause inconsistency in the current findings, including the pregnancy stage of Trp taken, its intensity, and pregnant women's age, eating habits, lifestyle, and health status. For example, in Wistar rats, the brain 5-HT concentration, TPH2 activity, and 5-HT uptake in offspring are decreased by fed a 10 g Trp-enriched diet from 2 weeks prior to mating through postnatal life [60] while administrated 30 mg/kg/day of Trp mixed with a stock chow diet for 1 week prior to mating increases total 5-HT metabolite content in the medulla at P20wk in the offspring of hypertensive rats [61]. Moreover, plasma Trp concentrations vary across maternal seasonality and season of conception [89]. Hence, the influence of the environment and other exogenous agents should be considered when studying the causality between maternal Trp fluctuation and neuropsychiatric development in offspring. The longitudinal studies of gestational Trp impacts are also advocated, because the early-life adversity can be masked by favorable experiences at a later age, such as family support, culture, and education [17].

6.2 The microbial barrier for investigating the fetal exposure on neuropsychiatric development

The maternal-fetal microbe transmission during pregnancy, vaginal delivery, and breastfeeding constitutes the initial gut microbiome in the progeny of humans and other viviparous mammals. Given the comorbid gastrointestinal symptoms of neurodevelopmental disorders [20], prenatal stimuli altering neurogenesis may have perturbed maternal-fetal microbe transmission and altered the gut microbiome and MGB axis functioning in the progeny [80, 81]. However, early-life predisposition can be buffered or masked by the postnatal life experience [17]. Hence, the later-life events, such as eating, diseases, medicine, may interrupt the offspring gut microbial development and veil the early-life effect on the MGB axis, as a barrier in the investigation of fetal exposure altering neuropsychiatric development [90].

6.3 Ethical issues in human and rodent research

Maternal Trp fluctuation potentially alters fetal brain and gastrointestinal development. However, it is not possible to determine fetal changes for logistical and ethical reasons in humans. Aborted fetuses from women undergoing pregnancy termination have been recruited to determine the neuroendocrinological alterations caused by maternal diseases or over-the-counter (OTC) and prescription drug administrations during pregnancy worldwide since 1973 [91]. However, a survey in 2012 revealed the fact that this kind of research is not likely to be approved by most North American medical institutions for ethical considerations [92]. Moreover, assessing fetal exposure effect is limited to a single cord plasma concentration measured at the time of delivery, i.e., real-time monitoring of fetal neuroendocrine profile is not allowed. However, in most clinical cases, the ratio of umbilical vein (UV) to maternal plasma (MP) does not reflect the exact fetal drug exposure relative to mother [93].

Rodents are widely used in preclinical pharmacologic research in assessing fetal exposure and investigating the underlying mechanisms, but the outcomes of experimental animal models have difficulty in extrapolating to clinical decisions. In viviparous animals, the variable litter size and gestational age cannot be accurately predicted; a great number of matings are needed to meet a certain sample size for sufficient statistical power; the female parent per se must be euthanized for sampling [90]. These go against the 3Rs of animal ethics, which advocate to minimize invasiveness, restrict animals subjected to potentially harmful procedures, and cut down the number of animals sacrificed, i.e., Replacement, Reduction, and Refinement [94].

7. Thinking chicken

7.1 Chicken embryo model

The advantages and disadvantages of human, rodent, and chicken models in investigating ontogenetic origin of neuropsychiatric disorders have been summarized in **Table 4**. The chicken embryo is a mainstay model for safety assessment in maternal-fetal medicine and mechanistic study due to its special biological characteristics: high reproducibility, time- and cost-saving preparation, self-contained development, precise litter size, accessibility, and easy in vivo experimental manipulation [95].

Species	Human	Rodent	Chicken
Advantages	• Closed to the clinical decisions • Equipped with placenta	• Accessibility • Approachable prenatal development • Equipped with placenta • Developing modern mechanistic approaches have been applied • Genetically engineered mouse models available	• Accessibility • Time- and cost-saving • High reproducibility providing sufficient sample size for statistical power • Precise litter size • Accurate developmental stages • Large embryos with a uniform genetic background • Easy in vivo experimental manipulation with the availability of a number of techniques • Self-sustained development
Disadvantages	• Ethical issues • Maternal metabolism influence • Maternal microbe transfer • Single time-point detection	• Sacrifice of the female parent • Unprecise and small litter size • Small embryos • Hard to predict the embryonic stage • Maternal metabolism influence • Maternal microbe transfer • Time-consuming and high cost	• Lack of placenta • Lack of developing modern mechanistic approaches • Lack of genetically engineered models

The table is adjusted based on [90].

Table 4.
A comparative summary among human, rodent, and chicken models in investigating ontogenetic origin of neuropsychiatric disorders.

Moreover, in viviparous animals, the placenta mediates the nutrient transfer between maternal and embryonic circulations [96]. The closed system prolongs chicken embryonic exposure to xenobiotics without excretion until hatching, reducing the stress caused by multiple injections in determining the toxic influence on fetal development and subsequent neuroendocrine alterations [97].

7.2 Chicken embryo for studying ontogenetic origin of neuropsychiatric disorders

As a sensitive target, heterogeneity exists in diverse brain regions at various embryonic stages, which is crucial for investigating ontogenetic origin of neuropsychiatric disorders, i.e., a dynamic and comprehensive perspective. In maternal-fetal medicine, the drug candidates need to be vigorously assessed using toxicological, pharmacokinetic, and pharmacological tests as well as electrophysiological, neurophysiological, and behavioral measures before clinical trials can begin. The chicken embryo model has been widely employed to investigate fetal neuropathology post antiepileptic exposure [95] as well as to determine neurotoxic effects of steroid hormones on the immature cerebellum [98].

Before hatching, the embryonic experience and genetic determinants have cooperated in developing postnatal cognition and behavior, which makes chickens central to understanding the interface between predisposition and experience-based learning at the beginning of life [99, 100]. A chick exhibits behavioral responses shortly after hatching via inherited predisposed and learning mechanisms, which shapes cognition [100]. Moreover, the large size of the chicken embryo and self-sustained embryonic development allow easy in vivo manipulation. The neurobiological basis underlying early social predispositions is being uncovered in chickens, and functional similarities have been identified between the brains of chickens and mammals [101]. For example, the avian forebrain is derived from the same anatomical substrate as mammals, demonstrating the cognitive similarity across species [102]. Hence, the chicken embryo offers a trustworthy and suitable model for investigating ontogenetic origin of neuropsychiatric disorders.

7.3 Embryonic serotonin exposure reduces aggression while embryonic tryptophan exposure yields bullying victims

The 5-HT and dopamine (DA) systems interact at a basic neurophysiological level in regulating impulsive aggression, which plays a critical role in several mental disorders, including BPD and antisocial personality disorder [103]. Similar to it in humans, aggression in chickens is related to personality disorders [104]. In ovo 5-HT injection (10 μg/egg) reduces aggressive behaviors at a cost of increased fearfulness during adolescence and before sex maturation in the White Leghorn chickens [105]. The results in the Dekalb XL birds, a highly aggressive strain [106, 107], indicate that prenatal 5-HT exposure (10 and 20 μg/egg) reduces aggression via regulating the 5-HT availability or DA storage and reprogramming the development of the HPA axis [11].

Bullying involvement is related to personality development [108]. Gut microbiota has a measurable impact on social performance via mediating the MGB axis; in turn, social interactions are involved in shaping the gut microbial community [109]. In a study, Trp administration (500 μg/egg) in White Leghorn chickens at E12 yields bullying victims, indicated by reduced body weight and aggressive behaviors in the male offspring before and during adolescence, attributing to the altered function of the MGB and HPA axes [12]. Briefly, the intestinal histomorphology has been altered in the Trp-treated roosters, i.e., the increased crypt depth and decreased villus/crypt ratio in the ileum-jejunum junction, indicating an altered gut microenvironment and reduced surface for absorbing nutrients. Corresponding changes in the cecal microbiota composition, i.e., the increased abundances of genera *Ruminococcaceae UCG-005*, *Olsenella*, *Ruminococcus_2*, and *Oscillospira*, have been identified in the Trp-treated roosters [12], which are the core microbes in human colonic crypt [110]. In this way, a low abundance of genus *Oscillospira* has been characterized in aggressive dogs compared with normal behavior group [111]. Moreover, a high abundance of genus *Olsenella* has been associated with low BW in the Japanese population and observed in female MDD patients [112, 113]. In the trier social stress test (TSST), peer victimization exhibits more stress with an altered HPA axis activity [114].The HPA axis is developmentally cross-linked with the gut microbiota [115], which hints the gut microbes' role in neurogenesis and behavioral development in offspring. Hence, the increased catecholamine concentrations in the chicken hypothalamus post embryonic Trp exposure indicate an altered HPA axis activity and may be associated with the altered gut microbiome and MGB axis function, mediating impulsive aggression confronting conflictual peer interactions [90].

8. Conclusions

This chapter discusses the relationship of TPH polymorphisms and Trp administrations with personality traits/disorders, which bridges the Trp metabolism in pregnant women and neuropsychiatric disorders in offspring. Gestational Trp participates in the development of the CNS and gastrointestinal system, which reciprocally interact via the MGB axis, shaping long-standing patterns of cognition and behavior. The chicken embryo can be a good model for investigating maternal effects on offspring neuropsychiatric development due to that it skirts the maternal influences on the neuroendocrine and gastrointestinal development, i.e., maternal metabolic fluctuation and maternal-fetal microbe transmission seen in humans and other mammals. Moreover, the behavioral response can be tested shortly after hatching due to social predispositions in chickens, which can be intervened during embryogenesis. Accumulated evidence in chicken embryonic development indicates that embryonic exposures to Trp and its metabolite, 5-HT, reprogram neuroendocrine and MGB axis in offspring, attenuating aggression and defeated in bullying. Herein, maintaining an appropriate Trp level by controlling dietary Trp and rigorous medication therapy during pregnancy has been advocated as a biotherapeutic targeting strategy for preventing personality disorders and comorbid psychosocial dysfunctions.

Author details

Xiaohong Huang[1,2*], Xiaohua Li[3] and Heng-Wei Cheng[2,4]

1 Department of Sports Medicine, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

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

3 School of Basic Medical Sciences, Qingdao University, Qingdao, Shandong, China

4 Livestock Behavior Research Unit, USDA-ARS, West Lafayette, IN, USA

*Address all correspondence to: ysrred@gmail.com

IntechOpen

References

[1] Asselmann E et al. The role of personality in the thoughts, feelings, and behaviors of students in Germany during the first weeks of the COVID-19 pandemic. PloS One. 2020;**15**(11):e0242904. DOI: 10.1371/journal.pone.0242904

[2] Björkenstam E et al. Association between childhood adversity and a diagnosis of personality disorder in young adulthood: a cohort study of 107,287 individuals in Stockholm County. European Journal of Epidemiology. 2017;**32**(8):721-731. DOI: 10.1007/s10654-017-0264-9

[3] Gartstein M, Skinner M. Prenatal influences on temperament development: the role of environmental epigenetics. Development and Psychopathology. 2018;**30**(4):1269-1303. DOI: 10.1017/s0954579417001730

[4] Brannigan R et al. The role of prenatal stress as a pathway to personality disorder: longitudinal birth cohort study. The British journal of Psychiatry: The Journal of Mental Science. 2020;**216**(2):85-89. DOI: 10.1192/bjp.2019.190

[5] Cackowski S et al. Anger and aggression in borderline personality disorder and attention deficit hyperactivity disorder - does stress matter? Borderline Personality Disorder and Emotion Dysregulation. 2017;**4**:6. DOI: 10.1186/s40479-017-0057-5

[6] Wilson ST et al. The tryptophan hydroxylase-1 A218C polymorphism is associated with diagnosis, but not suicidal behavior, in borderline personality disorder. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2009;**150**(2):202-208. DOI: 10.1002/ajmg.b.30788

[7] Zaboli G et al. Tryptophan hydroxylase-1 gene variants associate with a group of suicidal borderline women. Neuropsychopharmacology. 2006;**31**(9):1982-1990. DOI: 10.1038/sj.npp.1301046

[8] Perez-Rodriguez MM et al. Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. Journal of Psychiatric Research. 2010;**44**(15):1075-1081. DOI: 10.1016/j.jpsychires.2010.03.014

[9] Badawy AA-B. Tryptophan metabolism, disposition and utilization in pregnancy. Bioscience Reports. 2015;**35**(5):e00261. DOI: 10.1042/bsr20150197

[10] Huang X, Feng Z, Cheng H-w. Perspective: gestational tryptophan fluctuation altering neuroembryogenesis and psychosocial development. Cells. 2022;**11**(8):1270. DOI: 10.3390/cells11081270

[11] Huang X et al. Prenatal serotonin fluctuation affects serotoninergic development and related neural circuits in chicken embryos. Neuroscience. 2021;**473**:66-80. DOI: 10.1016/j.neuroscience.2021.08.011

[12] Huang X et al. Embryonic exposure to tryptophan yields bullying victimization via reprogramming the microbiota-gut-brain axis in a chicken model. Nutrients. 2022;**14**(3):661. DOI: 10.3390/nu14030661

[13] Kerekes N et al. ADHD, autism spectrum disorder, temperament, and character: phenotypical associations and etiology in a Swedish childhood

twin study. Comprehensive Psychiatry. 2013;**54**(8):1140-1147. DOI: 10.1016/j.comppsych.2013.05.009

[14] Rausch J et al. Associations between age and cortisol awakening response in patients with borderline personality disorder. Journal of Neural Transmission. 2021;**128**(9):1425-1432. DOI: 10.1007/s00702-021-02402-3

[15] Carrasco J et al. Hypothalamic-pituitary-adrenal axis response in borderline personality disorder without post-traumatic features. The British Journal of Psychiatry. 2007;**190**:357-358. DOI: 10.1192/bjp.bp.106.022590

[16] Tackett J et al. Personality × hormone interactions in adolescent externalizing psychopathology. Personality Disorders. 2014;**5**(3):235-246. DOI: 10.1037/per0000075

[17] Barker DJ. The fetal origins of adult disease. Fetal and Maternal Medicine Review. 1994;**6**(2):71-80. DOI: 10.1017/S0965539500001005

[18] Montgomery, A.K., et al., Maternal serotonin levels are associated with cognitive ability and core symptoms in autism spectrum disorder. Journal of the American Academy of Child & Adolescent Psychiatry, 2018. **57**(11): p. 867-875, doi: 10.1016/j.jaac.2018.06.025.

[19] Coste J et al. Risk of early neurodevelopmental disorders associated with in utero exposure to valproate and other antiepileptic drugs: a nationwide cohort study in France. Scientific Reports. 2020;**10**(1):17362. DOI: 10.1038/s41598-020-74409-x

[20] Kim J-W et al. Gastrointestinal tract abnormalities induced by prenatal valproic acid exposure in rat offspring. Toxicological Research. 2013;**29**(3):173-179. DOI: 10.5487/TR.2013.29.3.173

[21] De Angelis M et al. Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified. PloS One. 2013;**8**(10):e76993. DOI: 10.1371/journal.pone.0076993

[22] Bonnin A et al. A transient placental source of serotonin for the fetal forebrain. Nature. 2011;**472**(7343):347-350. DOI: 10.1038/nature09972

[23] Bonnin A et al. Serotonin modulates the response of embryonic thalamocortical axons to netrin-1. Nature Neuroscience. 2007;**10**(5):588-597. DOI: 10.1038/nn1896

[24] Joyce P et al. The presence of both serotonin 1A receptor (HTR1A) and dopamine transporter (DAT1) gene variants increase the risk of borderline personality disorder. Frontiers in Genetics. 2014;**4**:313. DOI: 10.3389/fgene.2013.00313

[25] Karahoda R et al. Dynamics of tryptophan metabolic pathways in human placenta and placental-derived cells: effect of gestation age and trophoblast differentiation. Frontiers in Cell and Developmental Biology. 2020;**8**:574034. DOI: 10.3389/fcell.2020.574034

[26] Anderson G, Maes M. Schizophrenia: linking prenatal infection to cytokines, the tryptophan catabolite (TRYCAT) pathway, NMDA receptor hypofunction, neurodevelopment and neuroprogression. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2013;**42**:5-19. DOI: 10.1016/j.pnpbp.2012.06.014

[27] Keane JM et al. Identifying a biological signature of prenatal maternal stress. JCI Insight. 2021;**6**(2):e143007. DOI: 10.1172/jci.insight.143007

[28] Tenhola S et al. Blood pressure, serum lipids, fasting insulin, and adrenal

hormones in 12-year-old children born with maternal preeclampsia. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**(3):1217-1222. DOI: 10.1210/jc.2002-020903

[29] Sun B et al. Association of preeclampsia in term births with neurodevelopmental disorders in offspring. JAMA Psychiatry. 2020;**77**(8):823-829. DOI: 10.1001/jamapsychiatry.2020.0306

[30] Law K et al. Tryptophan and purine metabolites are consistently upregulated in the urinary metabolome of patients diagnosed with gestational diabetes mellitus throughout pregnancy: a longitudinal metabolomics study of Chinese pregnant women part 2. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2017;**468**:126-139. DOI: 10.1016/j.cca.2017.02.018

[31] Rowland J, Wilson C. The association between gestational diabetes and ASD and ADHD: a systematic review and meta-analysis. Scientific Reports. 2021;**11**(1):5136. DOI: 10.1038/s41598-021-84573-3

[32] Notarangelo FM, Schwarcz R. Restraint stress during pregnancy rapidly raises kynurenic acid levels in mouse placenta and fetal brain. Developmental Neuroscience. 2016;**38**(6):458-468. DOI: 10.1159/000455228

[33] Galley JD et al. Prenatal stress-induced disruptions in microbial and host tryptophan metabolism and transport. Behavioural Brain Research. 2021;**414**:113471. DOI: 10.1016/j.bbr.2021.113471

[34] Kim S et al. The effects of serotonin transporter promoter and monoamine oxidase A gene polymorphisms on trait emotional intelligence. Neuropsychobiology. 2011;**64**(4):224-230. DOI: 10.1159/000327705

[35] Manuck S et al. Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. Biological Psychiatry. 1999;**45**(5):603-614. DOI: 10.1016/s0006-3223(98)00375-8

[36] Baud P et al. Modulation of anger control in suicide attempters by TPH-1. Genes, Brain, and Behavior. 2009;**8**(1):97-100. DOI: 10.1111/j.1601-183X.2008.00451.x

[37] Suzuki A et al. No association between the TPH A218C polymorphism and personality traits in Japanese healthy subjects. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2007;**31**(2):395-398. DOI: 10.1016/j.pnpbp.2006.10.003

[38] Yang J et al. Association between tryptophan hydroxylase 2 polymorphism and anger-related personality traits among young Korean women. Neuropsychobiology. 2010;**62**(3):158-163. DOI: 10.1159/000318572

[39] Cuartas Arias J et al. Exploring epistasis in candidate genes for antisocial personality disorder. Psychiatric Genetics. 2011;**21**(3):115-124. DOI: 10.1097/YPG.0b013e3283437175

[40] Rujescu D et al. Association of anger-related traits with SNPs in the TPH gene. Molecular Psychiatry. 2002;**7**(9):1023-1029. DOI: 10.1038/sj.mp.4001128

[41] Reuter M, Hennig J. Pleiotropic effect of the TPH A779C polymorphism on nicotine dependence and personality. American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics. 2005;**134**(1):20-24. DOI: 10.1002/ajmg.b.30153

[42] Tochigi M et al. No association of 5-HT2C, 5-HT6, and tryptophan hydroxylase-1 gene polymorphisms

with personality traits in the Japanese population. Neuroscience Letters. 2006;**403**:100-102. DOI: 10.1016/j.neulet.2006.04.020

[43] Laas K et al. Nice guys: homozygocity for the TPH2-703G/T (rs4570625) minor allele promotes low aggressiveness and low anxiety. Journal of Affective Disorders. 2017;**215**:230-236. DOI: 10.1016/j.jad.2017.03.045

[44] Lehto K et al. Effect of tryptophan hydroxylase-2 gene polymorphism G-703 T on personality in a population representative sample. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2015;**57**:31-35. DOI: 10.1016/j.pnpbp.2014.10.005

[45] Yoon H et al. Impact of tryptophan hydroxylase 2 G-703T polymorphism on anger-related personality traits and orbitofrontal cortex. Behavioural Brain Research. 2012;**231**(1):105-110. DOI: 10.1016/j.bbr.2012.03.001

[46] Gutknecht L et al. Tryptophan hydroxylase-2 gene variation influences personality traits and disorders related to emotional dysregulation. The International Journal of Neuropsychopharmacology. 2007;**10**(3):309-320. DOI: 10.1017/s1461145706007437

[47] Ward R et al. The role of serotonin in personality inference: tryptophan depletion impairs the identification of neuroticism in the face. Psychopharmacology. 2017;**234**(14):2139-2147

[48] Demoto Y et al. Neural and personality correlates of individual differences related to the effects of acute tryptophan depletion on future reward evaluation. Neuropsychobiology. 2012;**65**(2):55-64. DOI: 10.1159/000328990

[49] Wingrove J et al. Trait hostility and prolactin response to tryptophan enhancement/depletion. Neuropsychobiology. 1999;**40**(4):202-206. DOI: 10.1159/000026620

[50] Zimmermann M et al. The effects of acute tryptophan depletion on reactive aggression in adults with attention-deficit/hyperactivity disorder (ADHD) and healthy controls. PloS One. 2012;**7**(3):e32023. DOI: 10.1371/journal.pone.0032023

[51] Kanen JW et al. Serotonin depletion amplifies distinct human social emotions as a function of individual differences in personality. Translational Psychiatry. 2021;**11**(1):1-12. DOI: 10.1038/s41398-020-00880-9

[52] Cleare A, Bond A. The effect of tryptophan depletion and enhancement on subjective and behavioural aggression in normal male subjects. Psychopharmacology. 1995;**118**(1):72-81. DOI: 10.1007/BF02245252

[53] Feder A et al. Tryptophan depletion and emotional processing in healthy volunteers at high risk for depression. Biological Psychiatry. 2011;**69**(8):804-807. DOI: 10.1016/j.biopsych.2010.12.033

[54] Zepf F et al. Serotonergic functioning and trait-impulsivity in attention-deficit/hyperactivity-disordered boys (ADHD): influence of rapid tryptophan depletion. Human Psychopharmacology. 2008;**23**(1):43-51. DOI: 10.1002/hup.896

[55] Schmeck K et al. Mood changes following acute tryptophan depletion in healthy adults. Psychopathology. 2002;**35**(4):234-240. DOI: 10.1159/000063827

[56] Nesic J, Duka T. Effects of stress on emotional reactivity in hostile

heavy social drinkers following dietary tryptophan enhancement. Alcohol & Alcoholism. 2008;**43**(2):151-162. DOI: 10.1093/alcalc/agm179

[57] Concu A et al. Mental changes induced by the oral administration of tryptophan-free amino acid mixtures in man. IRCS Medical Science. 1977;**5**:520

[58] Moja E et al. Increase in stage 4 sleep after ingestion of a tryptophan-free diet in humans. Pharmacological Research Communications. 1984;**16**(9):909-914. DOI: 10.1016/s0031-6989(84)80027-2

[59] Young SN et al. Tryptophan depletion causes a rapid lowering of mood in normal males. Psychopharmacology. 1985;**87**(2):173-177. DOI: 10.1007/BF00431803

[60] Huether G, Thömke F, Adler L. Administration of tryptophan-enriched diets to pregnant rats retards the development of the serotonergic system in their offspring. Developmental Brain Research. 1992;**68**(2):175-181. DOI: 10.1016/0165-3806(92)90059-6

[61] Ito H et al. Effects of tryptophane on SHRSP offspring growth. Clinical and Experimental Hypertension. Part A: Theory and Practice. 1991;**13**(5):971-979. DOI: 10.3109/10641969109042103

[62] Arevalo R et al. Fetal brain serotonin synthesis and catabolism is under control by mother intake of tryptophan. Life Sciences. 1991;**49**(1):53-66. DOI: 10.1016/0024-3205(91)90579-z

[63] Martin L et al. Tryptophan ingestion by gestant mothers alters prolactin and luteinizing hormone release in the adult male offspring. Brain Research. 1997;**774**(1-2):265-268. DOI: 10.1016/s0006-8993(97)81718-0

[64] Fando JL, Domínguez F, Herrera E. Tryptophan overload in the pregnant rat: effect on brain amino acid levels and in vitro protein synthesis. Journal of Neurochemistry. 1981;**37**(4):824-829. DOI: 10.1111/j.1471-4159.1981.tb04467.x

[65] Imbesi R, Castrogiovanni P. Embryonic and postnatal development in experimental tryptophan deprived rats. A preliminary study. Journal of Molecular Histology. 2008;**39**(5):487-498. DOI: 10.1007/s10735-008-9188-8

[66] Imbesi R, Mazzone V, Castrogiovanni P. Is tryptophan 'more'essential than other essential aminoacids in development? A morphologic study. Anatomia, Histologia, Embryologia. 2009;**38**(5):361-369. DOI: 10.1111/j.1439-0264.2009.00955.x

[67] Flores-Cruz GM, Escobar A. Reduction of serotonergic neurons in the dorsal raphe due to chronic prenatal administration of a tryptophan-free diet. International Journal of Developmental Neuroscience. 2012;**30**(2):63-67. DOI: 10.1016/j.ijdevneu.2012.01.002

[68] Hsu C-N et al. Maternal tryptophan supplementation protects adult rat offspring against hypertension programmed by maternal chronic kidney disease: implication of tryptophan-metabolizing microbiome and aryl hydrocarbon receptor. International Journal of Molecular Sciences. 2020;**21**(12):4552. DOI: 10.3390/ijms21124552

[69] Castrogiovanni P et al. Effects of high-tryptophan diet on pre-and postnatal development in rats: a morphological study. European Journal of Nutrition. 2014;**53**(1):297-308. DOI: 10.1007/s00394-013-0528-4

[70] Bunce GE, Hess JL. Lenticular opacities in young rats as a consequence of maternal diets low in tryptophan and/

or vitamin E. The Journal of Nutrition. 1976;**106**(2):222-229. DOI: 10.1093/jn/106.2.222

[71] Penatti EM et al. Maternal dietary tryptophan deficiency alters cardiorespiratory control in rat pups. Journal of Applied Physiology. 2011;**110**(2):318-328. DOI: 10.1152/japplphysiol.00788.2010

[72] Xu K et al. Negative effects on newborn piglets caused by excess dietary tryptophan in the morning in sows. Journal of the Science of Food and Agriculture. 2019;**99**(6):3005-3016. DOI: 10.1002/jsfa.9514

[73] Zoratto F et al. Effects of maternal L-tryptophan depletion and corticosterone administration on neurobehavioral adjustments in mouse dams and their adolescent and adult daughters. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2011;**35**(6):1479-1492. DOI: 10.1016/j.pnpbp.2011.02.016

[74] Delahanty D, Raimonde A, Spoonster E. Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biological Psychiatry. 2000;**48**(9):940-947. DOI: 10.1016/s0006-3223(00)00896-9

[75] Wirth M et al. The effect of cortisol on emotional responses depends on order of cortisol and placebo administration in a within-subject design. Psychoneuroendocrinology. 2011;**36**(7):945-954. DOI: 10.1016/j.psyneuen.2010.11.010

[76] Atmaca M et al. Increased serum prolactin in borderline personality disorder. The International Journal of Psychiatry in Medicine. 2015;**49**(3):169-175. DOI: 10.1177/0091217415582172

[77] Rutkowski K et al. Hyper-prolactinemia phenomenon in neurotic and personality disorders and changes in prolactin level after the psychotherapy. European Psychiatry. 2017;**41**(S1):S260-S260. DOI: 10.1016/j.eurpsy.2017.02.067

[78] Lennartsson A-K, Jonsdottir IH. Prolactin in response to acute psychosocial stress in healthy men and women. Psychoneuroendocrinology. 2011;**36**(10):1530-1539. DOI: 10.1016/j.psyneuen.2011.04.007

[79] Deuter C et al. Psychosocial stress increases testosterone in patients with borderline personality disorder, post-traumatic stress disorder and healthy participants. Borderline Personality Disorder and Emotion Dysregulation. 2021;**8**(1):3. DOI: 10.1186/s40479-021-00145-x

[80] Usui N, Matsuzaki H, Shimada S. Characterization of early life stress-affected gut microbiota. Brain Sciences. 2021;**11**(7):913. DOI: 10.3390/brainsci11070913

[81] Rincel M et al. Multi-hit early life adversity affects gut microbiota, brain and behavior in a sex-dependent manner. Brain, Behavior, and Immunity. 2019;**80**:179-192. DOI: 10.1016/j.bbi.2019.03.006

[82] Cheng H-w, Jiang S, Hu J. Gut-brain axis: probiotic, *Bacillus subtilis*, prevents aggression via the modification of the central serotonergic system. In: Mahmoudi R, Moosazad S, Aghaei K, editors. Oral Health by Using Probiotic Products. London, UK: IntechOpen; 2019

[83] Szyszkowicz JK et al. Implications of the gut microbiota in vulnerability to the social avoidance effects of chronic social defeat in male mice. Brain, Behavior, and

Immunity. 2017;**66**:45-55. DOI: 10.1016/j.bbi.2017.06.009

[84] Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Developmental Psychobiology. 1999;**35**(2):146-155

[85] Devoe LD et al. Maternal dietary substrates and human fetal biophysical activity: I. The effects of tryptophan and glucose on fetal breathing movements. American Journal of Obstetrics and Gynecology. 1986;**155**(1):135-139. DOI: 10.1016/0002-9378(86)90096-7

[86] Farzi A, Fröhlich E, Holzer P. Gut microbiota and the neuroendocrine system. Neurotherapeutics. 2018;**15**(1):5-22. DOI: 10.1007/s13311-017-0600-5

[87] Seidman LJ et al. The relationship of prenatal and perinatal complications to cognitive functioning at age 7 in the New England Cohorts of the National Collaborative Perinatal Project. Schizophrenia Bulletin. 2000;**26**(2):309-321. DOI: 10.1093/oxfordjournals.schbul.a033455

[88] Entringer S. Prenatal stress exposure and fetal programming of complex phenotypes: interactive effects with multiple risk factors. Neuroscience and Biobehavioral Reviews. 2020;**117**:3-4. DOI: 10.1016/j.neubiorev.2020.04.002

[89] Levitan RD et al. Seasonality of plasma tryptophan and kynurenine in pregnant mothers with a history of seasonal affective disorder: vulnerability or adaptation? The World Journal of Biological Psychiatry. 2020;**21**(7):529-538. DOI: 10.1080/15622975.2020.1769189

[90] Huang X, Cheng H-w. Perspective: chicken models for studying the ontogenetic origin of neuropsychiatric disorders. Biomedicines. 2022;**10**(5):1115. DOI: 10.3390/biomedicines10051155

[91] Cates W, Grimes DA, Schulz KF. The public health impact of legal abortion: 30 years later. Perspectives on Sexual and Reproductive Health. 2003;**35**(1):25-28. DOI: 10.1363/3502503

[92] Gedeon C, Nava-Ocampo AA, Koren G. Ethical issues in pharmacologic research in women undergoing pregnancy termination: a systemic review and survey of researchers. Obstetrics and Gynecology International. 2012;**2012**:724591. DOI: 10.1155/2012/724591

[93] Zhang Z et al. Development of a novel maternal-fetal physiologically based pharmacokinetic model I: insights into factors that determine fetal drug exposure through simulations and sensitivity analyses. Drug Metabolism and Disposition. 2017;**45**(8):920-938. DOI: 10.1124/dmd.117.075192

[94] Cheluvappa R, Scowen P, Eri R. Ethics of animal research in human disease remediation, its institutional teaching; and alternatives to animal experimentation. Pharmacology Research & Perspectives. 2017;**5**(4):e00332. DOI: 10.1002/prp2.332

[95] Zosen D et al. Chicken embryo as animal model to study drug distribution to the developing brain. Journal of Pharmacological and Toxicological Methods. 2021;**112**:107105. DOI: 10.1016/j.vascn.2021.107105

[96] Zohn IE, Sarkar AA. The visceral yolk sac endoderm provides for absorption of nutrients to the embryo during neurulation. Birth Defects Research Part A: Clinical and Molecular Teratology. 2010;**88**(8):593-600. DOI: 10.1002/bdra.20705

[97] Bjørnstad S et al. Cracking the egg: potential of the developing chicken as a model system for nonclinical safety studies of pharmaceuticals. Journal of Pharmacology and Experimental Therapeutics. 2015;**355**(3):386-396. DOI: 10.1124/jpet.115.227025

[98] Aden P et al. Low-potency glucocorticoid hydrocortisone has similar neurotoxic effects as high-potency glucocorticoid dexamethasone on neurons in the immature chicken cerebellum. Brain Research. 2008;**1236**:39-48. DOI: 10.1016/j.brainres.2008.07.095

[99] Rosa-Salva O et al. Sensitive periods for social development: interactions between predisposed and learned mechanisms. Cognition. 2021;**213**:104552. DOI: 10.1016/j.cognition.2020.104552

[100] De Haas EN et al. Prenatal and early postnatal behavioural programming in laying hens, with possible implications for the development of injurious pecking. Frontiers in Veterinary Science. 2021;**8**:693. DOI: 10.3389/fvets.2021.678500

[101] Marino L. Thinking chickens: a review of cognition, emotion, and behavior in the domestic chicken. Animal Cognition. 2017;**20**(2):127-147. DOI: 10.1007/s10071-016-1064-4

[102] Jarvis ED et al. Avian brains and a new understanding of vertebrate brain evolution. Nature Reviews Neuroscience. 2005;**6**(2):151-159. DOI: 10.1038/nrn1606

[103] Seo D, Patrick C, Kennealy P. Role of serotonin and dopamine system interactions in the neurobiology of impulsive aggression and its comorbidity with other clinical disorders. Aggression and Violent Behavior. 2008;**13**(5):383-395. DOI: 10.1016/j.avb.2008.06.003

[104] Daigle C et al. Individual consistency of feather pecking behavior in laying hens: once a feather pecker always a feather pecker? Frontiers in Veterinary Science. 2015;**2**:6. DOI: 10.3389/fvets.2015.00006

[105] Dennis RL, Fahey AG, Cheng H-w. Alterations to embryonic serotonin change aggression and fearfulness. Aggressive Behavior. 2013;**39**(2):91-98. DOI: 10.1002/ab.21459

[106] Dennis R, Cheng H-w. The dopaminergic system and aggression in laying hens. Poultry Science. 2011;**90**(11):2440-2448. DOI: 10.3382/ps.2011-01513

[107] Cheng H-w, Muir W. Chronic social stress differentially regulates neuroendocrine responses in laying hens: II. Genetic basis of adrenal responses under three different social conditions. Psychoneuroendocrinology. 2004;**29**(7):961-971. DOI: 10.1016/j.psyneuen.2003.09.002

[108] Antila H et al. Bullying involvement in relation to personality disorders: a prospective follow-up of 508 inpatient adolescents. European Child & Adolescent Psychiatry. 2017;**26**(7):779-789. DOI: 10.1007/s00787-017-0946-6

[109] Johnson K. Gut microbiome composition and diversity are related to human personality traits. Human Microbiome Journal. 2020;**15**:100069. DOI: 10.1016/j.humic.2019.100069

[110] Saffarian A et al. Crypt-and mucosa-associated core microbiotas in humans and their alteration in colon cancer patients. MBio. 2019;**10**(4):e01315-e01319. DOI: 10.1128/mBio.01315-19

[111] Mondo E et al. Gut microbiome structure and adrenocortical activity

in dogs with aggressive and phobic behavioral disorders. Heliyon. 2020;**6**(1):e03311. DOI: 10.1016/j.heliyon.2020.e03311

[112] Andoh A et al. Comparison of the gut microbial community between obese and lean peoples using 16S gene sequencing in a Japanese population. Journal of Clinical Biochemistry and Nutrition. 2016;**59**(1):65-70. DOI: 10.3164/jcbn.15-152

[113] Chen J et al. Sex differences in gut microbiota in patients with major depressive disorder. Neuropsychiatric Disease and Treatment. 2018;**14**:647-655. DOI: 10.2147/ndt.S159322

[114] Knack JM, Jensen-Campbell LA, Baum A. Worse than sticks and stones? Bullying is associated with altered HPA axis functioning and poorer health. Brain and Cognition. 2011;**77**(2):183-190. DOI: 10.1016/j.bandc.2011.06.011

[115] Berthoud H-R, Albaugh VL, Neuhuber WL. Gut-brain communication and obesity: understanding functions of the vagus nerve. Journal of Clinical Investigation. 2021;**131**(10):e143770. DOI: 10.1172/JCI143770