Review

Tryptophan Metabolism in Developmental Origins of Health and Disease (DOHaD)

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Review

Tryptophan Metabolism in Developmental Origins of Health and Disease (DOHaD)

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Abstract: Tryptophan, an essential amino acid in mammals obtained from the diet, is influenced by maternal diet, which impacts early life and development of offspring. This is studied under the Developmental Origins of Diseases and Health (DOHaD) concept, so factors from conception to early childhood affect health and disease susceptibility. Tryptophan is metabolized mainly through two pathways: serotonin (5-HT) and kynurenine. The kynurenine pathway, active in the brain, gut, liver, and placenta, breaks down over 95% of tryptophan and plays roles in inflammation, neurotransmission, immune responses, and immune modulation during pregnancy. The serotonin pathway uses up to 5% of Tryptophan, mainly in the gut, adipose tissues, pancreatic cells, and central nervous system, and regulates responses to environmental changes, including sleep, cognition, and feeding behavior. Key enzymes in these pathways include Trp-2,3-dioxygenase (TDO), indoleamine-2,3-dioxygenase (IDO) type1 (IDO1), and type 2 (IDO2) (kynurenine pathway), and tryptophan hydroxylase type 1 (TPH1) and type 2 (TPH2), serotonin pathway. The fetus-placental unit manages tryptophan metabolism. Serotonin and kynurenine are crucial for placental health and fetal development. Serotonin adjusts placental blood volume and aids neurodevelopment. Kynurenine metabolites protect the fetus from maternal immunity and offer initial neuroprotection. At birth, infants switch from placental nutrients to breast milk, rich in tryptophan and protective bioactive molecules. Tryptophan, solely from breast milk, is crucial for infants. Its levels are high in newborns (first three weeks, 2-4 times higher than in adults), gradually declining to adult levels by the fourth week. The highlights the importance of tryptophan for the serotonin and kynurenine pathways in fetuses, newborns and babies applied to the DOHaD concept.

Keywords: tryptophan; serotonin; DOHaD; kynurenine

1. Introduction

Billions of years ago, the Earth probably had an inhospitable landscape full of inorganic chemical elements. Many minerals and gases, such as carbon dioxide, were already present. Perhaps due to a fortuitous temporal conjunction of factors, chemical reactions in this hostile environment triggered the emergence of molecules and the very complex interactions between them, which laid the foundations for the beginning of life, the first cell. Somehow, the chemical reactions on this primitive Earth also produced molecules that began to self-replicate. Most origins of life researchers believe that RNA was the first self-replicating molecule to form. Self-replication is a property of living beings that is still an open question. The thousands of unicellular and multicellular living beings we know today are distinct and overly complex. However, all their cells are synthesized from common elements, both atomic (carbon, hydrogen, oxygen, nitrogen, etc.) and molecular (water, glycids, lipids, proteins). Proteins in living beings are the machinery by which cells conduct their functions. They are made up of amino acids that gradually appeared on primitive Earth. Due to its molecular weight and complexity, the amino acid tryptophan, an indolamine, is thought to have been among the last to originate [1]. This amino acid is essential in the structure and function of many proteins

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and is also a precursor of several key molecules in the physiology of various organisms. In mammals, including humans, tryptophan is an essential amino acid that must be obtained from diet and is, therefore, strongly influenced by environmental factors, particularly the diet at the beginning of life, which strongly influences development [1].

These aspects have been discussed in recent years from the perspective of the DOHaD concept. The DOHaD investigators propose that environmental, phylogenetic, maternal, fetal/infant growth and development factors acting throughout life, particularly at the time of conception, during fetal life, infancy, and early childhood, have an impact on health and susceptibility to disease [2]. It is now known that during the first stages of mammalian life, the still-forming organism interacts with numerous environmental stimuli that may or may not express its best growth and developmental potential. This ability of the same genotype in these individuals, interacting with the environment, to express different phenotypes is called phenotypic plasticity. It allows adaptation to environmental variations outside the context of natural selection. Thus, the same genetic profile can develop, adapting to various conditions. The phenotypic plasticity of development is the main basis of the events in this perinatal phase. The formation of an organism is plastic in its response to environmental challenges, with adaptations occurring during development in different metabolic pathways, cells, tissues, organs, and systems; in the latter, particularly the nervous system, since it has an early window of great vulnerability which corresponds to the first 2-3 years of life in humans. During adaptive processes, there may be a conflict between environmental stimuli and preprogrammed metabolic pathways, leading to pathologies that may manifest in adulthood [3]. A study by Ravelli et al. in the 1970s of the children of pregnant women who experienced a food shortage provided us with valuable information [4]. There is a relationship between gestational (first trimester) malnutrition and obesity in adulthood. Baker et al. (2002) [5] then linked an adverse nutritional environment during intrauterine life and childhood to cardiovascular disease in adulthood. They found that children with low birth weight had higher blood pressure and were more likely to develop type 2 diabetes. Subsequently, other theories appeared that tried to explain the consequences of phenotypic plasticity on development. Epigenetic events are highly relevant to DOHaD studies because they are the interface between the environment, the genotype, and the phenotypic expression of the individual during development [6]. Today, we understand the phenomenon of phenotypic plasticity with the molecular basis of epigenetics, and studies have explained some of the consequences of early life adversity that later manifest in adult disease. Pathologies in adulthood, such as metabolic syndrome, obesity, and mental disorders (Depression and Anxiety), may have their origins associated with insults in early life [7–9] Several environmental factors can affect human development, but the best understood are nutritional factors early in life [6,10,11]. Organisms that have been subjected to perinatal malnutrition or overnutrition show dyslipidemia, diabetes, and obesity in adulthood, as well as emotional disorders such as depression and anxiety [4,9,12–15]. In the nervous system, one of the neurotransmission systems most affected by environmental variation in early life, resulting in discordant patterns in adulthood, is serotonin, whose precursor amino acid is tryptophan [16–18]. The metabolism of tryptophan produces various functionally active substances in the nervous system, some neuroprotective, others neurotoxic [19]. However, the relationship between tryptophan and nervous system development is poorly understood in scientific literature. Only in 2000 did the first article characterize the messenger RNA of tryptophan hydroxylase, the enzyme limiting serotonin synthesis, from developing rat brains [20]. In the context of DOHaD, this enzyme has been found to be upregulated in adolescents and adult organisms subjected to neonatal stress [21]. Tryptophan-deficient diets during pregnancy result in lower offspring body temperatures, reduced ventilatory responses to CO2, and slower heart rates [22]. Physiological changes in tryptophan availability for serotonin synthesis are associated with sudden infant death syndrome [23]. A maternal diet deficient in tryptophan during lactation promotes emotional disturbances in adult offspring. The mother was offered a low tryptophan diet from day 1 to day 8 of lactation, and behaviour was analyzed for anxiety and anhedonia in the adult offspring. They found decreased motivation and exploration of a new environment, anhedonia, and neurochemical changes in the prefrontal cortex (decreased dopamine and serotonin levels) [24]. As explained above, the

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metabolism of tryptophan, its main metabolic pathways, its metabolism for the mother/newborn binomial, its epigenetics, and its metabolism; all these aspects in the light of DOHAD and in neurodevelopment, are the topics that we will discuss in this review.

2. Tryptophan Metabolism in Mammals

Tryptophan was discovered by Hopkins and Cole in 1901 as a substance that could only be detected by enzymes or alkaline hydrolysates of proteins. It was the first amino acid to be considered essential. The name tryptophan comes from the fact that it is revealed by the tryptic digestion of a protein [25]. Tryptophan is an aromatic amino acid produced by bacteria in the shikimate pathway from phosphoenol pyruvate and erythrose-4-phosphate into chorismate, following a seven-step pathway to the production of chorismate, the precursor of tryptophan [26]. This pathway is not found in animals, so tryptophan is an essential amino acid [25]. Tryptophan is the unique protein amino acid derived from Indol, a bicyclic ring formed by a benzene group and a pyrrole group (L-Trp), linked to the α carbon by an a-CH2 group. The presence of the indole ring gives this molecule highly hydrophobic properties [27].

Approximately 90% of tryptophan in the bloodstream is bound to albumin, and only 10% is free. Free tryptophan competes to cross the blood-brain barrier and enter the brain with other neutral amino acids (tyrosine, phenylalanine, leucine, isoleucine, and valine). Among the five competing amino acids, tryptophan has the lowest plasma concentration [28]. In the body, as well as being a part of protein synthesis, it is an obligatory substrate to produce important bioactive substances such as kynurenine, serotonin, and melatonin. Several pathways metabolize tryptophan, the most important being the methoxy-indol pathway, which produces serotonin (0-5%), and the kynurenine pathway (95%), which produces neuroprotective molecules, including kynurenic and picolinic acids, nicotinamide adenine dinucleotide (NAD^+), and neurotoxic molecules including quinolinic acids and 3-hydroxykynurenine [19].

The primary pathway for tryptophan metabolism is the Kyn pathway, which is responsible for breaking down over 95% of tryptophan into several bioactive compounds [29]. This pathway plays roles in inflammation, excitatory neurotransmission, and immune responses, and it may also contribute to immune modulation during pregnancy to prevent rejection of the fetus [30]. Key enzymes in the Kyn pathway are TDO, IDO1 and IDO2 [31]. Their activity is influenced by glucocorticoids or proinflammatory cytokines, respectively [32]. IDO is found in various human organs like the brain, gastrointestinal tract, liver, and placenta, whereas TDO is mainly expressed in the liver [33].

In the central nervous system, the kynurenine pathway is predominantly active in astrocytes (producing kynurenic acid, KYNA) and microglia (producing quinolinic acid, QA) [34]. Notably, TDO is more abundant in astrocytes, activated by glucocorticoids, while IDOs are more prevalent in microglia, activated by proinflammatory cytokines [35–37]. Tryptophan undergoes conversion into N-formyl kynurenine (NFK) by IDO1, IDO2, and TDO enzymes, which is then transformed into kynurenine (kyn) by arylformamidase (AFMID). Kyn is then metabolized in three stages. First, Kyn aminotransferases (KAT I–IV) convert Kyn to kynurenic acid (KYNA), which acts as a noncompetitive N-methyl-D-aspartic acid (NMDA) glutamate receptor antagonist and an endogenous antioxidant, inhibiting excitotoxicity and neuroinflammation. Second, kynureninase (KYNU) catalyzes the conversion of Kyn to anthranilic acid (AA). Third, kynurenine-3-monooxygenase (KMO) transforms Kyn into 3-hydroxykynurenine (3-HK). KYNU converts 3-HK into 3-hydroxy anthranilic acid (3-HAA) and alanine, while KAT converts 3-HK into xanthurenic acid (XA). Additionally, alanine undergoes transamination to pyruvate, and 3-HAA is converted to neurotoxic quinolinic acid (QA) by 3-hydroxyanthranilate-3,4-dioxygenase (HAAO). QA is then converted to NAD^+ by QA phosphoribosyltransferase (QAPRT). The 3-HK can lead to neuronal degeneration and apoptosis, QA is linked to Alzheimer's disease (AD), depression, and schizophrenia, while NAD^+ serves as an essential coenzyme in energy metabolism, contributing to cell division and mitochondrial functions [33] (Figure 1).

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The serotonin pathway is integral to numerous physiological processes and plays crucial roles throughout the body. Tryptophan can be transformed into 5-hydroxytryptophan (5-HTP) by TPH1 in enterochromaffin cells of the gastrointestinal tract (GUT), in brown (BAT) and white (WAT) adipose tissues, β-cell pancreatic cells, and by TPH2 in central neurons [38]. Subsequently, 5-HTP is converted into 5-hydroxytryptamine (5-HT) by aromatic L-amino acid decarboxylase with the cofactor pyridoxal-5-phosphate. The 5-HT, also known as serotonin, is a monoamine neurotransmitter in the human central nervous system and can cause vascular smooth muscle contraction when present in the blood. It plays a pivotal role in regulating adaptive responses and responses to environmental changes, including sleep, cognition, and feeding behaviour [33,38]. The TPH1 primarily synthesizes peripheral serotonin in enterochromaffin cells and is then stored in platelets. However, serotonin produced in the gut cannot cross the blood-brain barrier or regulate central nervous system functions. Consequently, neurons in the brain stem's raphe nuclei express TPH2, promoting serotonin synthesis in the central nervous system [33,38]. serotonin is further converted into 5-Hydroxyindoleacetic acid (5-HIAA), the primary serotonin metabolite, which is excreted via the kidneys or can be further converted into melatonin, regulating the sleep-wake cycle [33]. Additionally, the biological functions of serotonin rely on the distinct 14 subtypes of serotonin receptors found in various cells and tissues [33,38]. It has also been reported that serotonin in the gut plays a part in melatonin production [39].

In the indole pathways, the gut microbiota plays a crucial role in tryptophan metabolism by directly converting tryptophan into various molecules like indole and its derivatives. These substances help keep intestinal balance by regulating the expression of proinflammatory and anti-inflammatory cytokines [33,40]. The gut microbiota converts a small part of tryptophan into indole and its derivatives, including indoleacrylic acid, indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), indole-3-acetaldehyde (3-IAld), and tryptamine [41]. Specific bacteria like Anaerostipes, Bacteroides, Clostridium, Bifidobacterium, and Lactobacillus break down tryptophan into indole derivatives. For example, Clostridium sporogenes and Ruminococci convert tryptophan to tryptamine, while Lactobacillus metabolizes tryptophan into indole-3-carboxaldehyde (I3A). Other bacteria like Pseudomonas, Staphylococcus, and Providencia ease the conversion of tryptophan to kynurenine.[42]

Indole and its derivatives play significant roles in gastrointestinal function, inflammation control, antioxidation, and immune system regulation. Indole, for instance, promotes the release of glucagon-like peptide-1, which slows down gastric emptying and reduces appetite. Tryptamine encourages the secretion of serotonin from enterochromaffin cells, stimulating gastrointestinal movement by influencing intestinal neurons [33,42,43].

The authors, Perez-Castro in 2023 [44] believe that the role of Trp and its metabolites in growth and homeostasis is only beginning to be understood [44]. The enzymes that limit tryptophan metabolism, IDO, TDO, KMO and TPH, are current targets of therapeutic strategies for treating diseases [45–49].

3. Main Pathways of Tryptophan Metabolism in the Foetus

The fetus-placental unit presents a coordinated metabolization of tryptophan, essential to ensure adequate fetal development. The fetus has unique needs for tryptophan and its active metabolites during development. These are relevant to placentation, immune regulation, and fetal development [50,51]. The metabolites serotonin and kynurenine play important roles in the placenta during pregnancy [52].

Tryptophan metabolism affects the health of the placenta and fetus based on the different activities of its metabolites. Serotonin, being a vasoconstrictive substance, can modulate blood volume to the placenta and act to enable trophoblasts, in addition to its vital role in neurodevelopment. On the other hand, when tryptophan is metabolized in the kynurenine pathway, it protects the fetus from maternal immunity [30] and produces neuroprotective metabolites initially.

Since 2011, it has been known in rodents [53] and humans [50] that tryptophan is metabolized in the placenta to produce serotonin during pregnancy. In the tryptophan metabolism during

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pregnancy, the serotonin pathway produces serotonin and melatonin, essential for fetal development. The placenta is a barrier to the passage of serotonin to the fetus during a certain period of pregnancy; it also acts as a transient source of serotonin from a maternal tryptophan precursor [53]. It has been seen that before the fetal nervous system produces serotonin, it already acts effectively on neuronal growth and migration. Evidence was obtained through an experiment in which the placenta was isolated, and the uterine artery was cannulated to inject tryptophan into it. On the opposite side, in the umbilical vein, there was an accumulation of newly synthesized serotonin. This proved that the living placenta can convert tryptophan to serotonin and release the neurotransmitter into the fetal circulation [53]. However, when serotonin was injected into the uterine artery, only 1% of serotonin was produced on the fetal side, showing that production was placental and dependent on tryptophan [53]. A few years later, researchers saw that serotonin production occurs through syncytiotrophoblasts, cytotrophoblasts, and villous nuclei in a pathway involving placental serotonin transporters, gap junctions, organic cation transporters (OCT3), and monoamine oxidase (MAO) [54]. The first evidence in this context showed that placental OCT3 extracts serotonin from the fetus in placental trophoblastic cells, where it is degraded by MAO [55]. Any interruption of OCT3 could alter fetal serotonin dynamics [55]. To keep fetal-placental serotonergic homeostasis, the mechanism of serotonin uptake by the placenta has been studied. During the first trimester of pregnancy, co-expression of the two isoforms of tryptophan hydroxylase, the limiting enzymes for serotonin synthesis, is seen in trophoblast cells and decidual cells in the human placenta [56]. Late in pregnancy, the placenta metabolizes excess serotonin by the enzyme MAO, producing 5-HIAA [55].

The placenta controls serotonin levels for the fetus, and disruption of placental serotonergic pathways by various insults can severely impair fetal development [57]. These insults have harmful effects depending on the period in which they occur. For example, when there is placental insufficiency, there is a reduction in the levels of melatonin, a direct metabolite of serotonin, resulting in fetal growth restriction [58]. These findings of placental uptake of extra serotonin into the fetus highlight homeostatic control mechanisms during fetal development. These mechanisms may help to modulate developmental perturbations in serotonin signalling [59].

Melatonin (N-acetyl-5-methoxy tryptamine), an indole derived from tryptophan, plays a crucial role in the functioning of the human placenta [60] and is essential to producing trophoblast villi and their attachment to the endometrium. Melatonin synthesis enzymes are found in trophoblast villi in the human placenta [60]. In the placenta, melatonin plays a part in the development, growth, differentiation, and function of lymphatic tissue [61].

In addition to the serotonin pathway, the placenta has the kynurenine pathway's components. Approximately 95% of tryptophan is metabolized to kynurenine [19]. The enzymes tryptophan 2,3-dioxygenase (TDO) and IDO are limiting steps in the kynurenine synthesis pathway from tryptophan. During pregnancy, a decrease in blood tryptophan concentrations and an increase in kynurenine and IDO expression and function have been seen in mothers [62]. Depending on the gestation period, the TDO and IDO enzymes exert synergistic and differentiated functions.

Early in pregnancy, the enzyme TDO can be expressed at elevated levels in the placenta [63]. An elevated level of early tryptophan metabolizing activity via TDO has been detected in the placenta, indicating that IDO is not present in the early stages of development and that its action in this function is exerted by placental TDO [55]. It was only reported in the 1990s that the placental IDO enzyme may be involved in regulating the maternal immune system's response in early pregnancy [30]. Thus, the administration of 1-methyltryptophan, an IDO inhibitor, led to maternal T-cell-induced rejection of the fetus [30]. The IDO protects the fetus from lethal maternal immunity, and transient expression in the placenta may be necessary to induce maternal immune tolerance [30].

Recently, some authors have suggested that because of the important role of tryptophan metabolism during fetal development, it is necessary to ensure an essential balance of these molecules between the fetus and the placenta to guarantee proper brain development since any environmental insult that may affect this axis, such as drugs or diseases, may affect the organized and temporal functioning of the enzymes involved in tryptophan metabolism [64], which may contribute to understanding the

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DOHaD. A 2009 study was the first to prove that TDO enzyme deficiency in the embryo can affect systemic tryptophan metabolism, neurogenesis, and anxiety-related behaviour in vivo [65].

The enzymes involved in the kynurenine pathway within the placenta have been studied more extensively than their metabolites. However, our understanding of the relationship between these metabolites produced in the kynurenine pathway and fetal life is still limited. Existing research primarily associates the presence of these metabolites with diseases in adulthood.

One notable metabolite is quinolinic acid, which tends to be elevated in patients with schizophrenia, a neurodevelopmental disorder. Interestingly, quinolinic acid and 3-hydroxyquinolinic acid levels are also high during fetal life, but they decrease significantly at birth [66]. These findings suggest distinct roles for these metabolites during fetal development.

The increased levels of quinolinic acid have a negative impact on the release of essential neurotransmitters crucial for neurodevelopment, including GABA, dopamine, acetylcholine, and glutamate. Furthermore, supplementation with L-kynurenine sulfate (100 mg/day) during pregnancy, administered through the maternal diet, elevates quinolinic acid levels in the fetal brain. This supplementation leads to reduced gene expression of α7nAch and mGLUR2 receptors, decreased dendritic spine density in the prefrontal cortex, and cognitive deficits seen throughout the offspring's adult life [67].

In summary, the expression of enzymatic proteins involved in tryptophan metabolism during gestation may play a crucial role in deciding health and disease patterns in adulthood.

4. Tryptophan Metabolism in the Human Newborn

At birth, newborns are exclusively fed by their mothers. There is much evidence of the association between maternal nutrition, whether adequate or not, and the availability of nutrients for the newborn, which can trigger pathologies in adult life.

The baby transfers its nutrient source from the placenta to breast milk at birth. This essential fluid has bioactive molecules such as cytokines, which elevate levels of tryptophan and protect the newborn with maternal immunity [68]. Breast milk is the only source of tryptophan for infants. The concentration of free tryptophan in breast milk changes with the age of the infant, and this is presumably done to meet the infant's changing needs. Quantified tryptophan in breast milk at different ages after birth and found a decrease in free and total tryptophan over the days of lactation [69]. On the 30th day of lactation, the total fraction averages 8.9 mg/L, and the free fraction averages 6.3 mg/L; on the 100th day, 1.3 and 1.1 mg/L, respectively. The first milk in the first 24 and 96 hours after birth is defined as colostrum, distinct in composition, appearance and volume and rich in immunologic components [70]. The colostrum from preterm mothers had higher levels of total tryptophan but lower levels of free tryptophan compared to term mothers [71].

There is compelling evidence that the availability of tryptophan to infants can directly influence their brain serotonin levels. A study found that plasma tryptophan levels differed in infants who consumed human milk, formula, and cow's milk. The availability of tryptophan to the serotonin or kynurenine pathways in the plasma and in the brain varies depending on the amount of tryptophan consumed and the amount of other neutral amino acids that compete with tryptophan for passage across the blood-brain barrier.

It was also seen that the levels of the metabolite's kynurenine and kynurenic acid and the kynurenine/tryptophan ratio increased from day 7 to day 14 of life only in preterm mothers' milk [71]. A study confirmed the measurement of tryptophan and kynurenine levels in colostrum from mothers during the first 24 hours after birth. Concentrations of 17.3μM tryptophan and 0.45μM kynurenine were found [72]. Only in 2018 did the first study examine the levels of free tryptophan, kynurenine, and kynurenic acid in the milk of mothers with preterm birth and the relationship between these molecules, stress, and maternal immune status. This study of 24 mothers (12 term and 12 preterm) found that the milk of mothers with preterm babies had higher levels of total tryptophan but lower levels of free tryptophan compared to term mothers [71]. It was also observed that the levels of the metabolite's kynurenine and kynurenic acid and the kynurenine/tryptophan ratio increased from day 7 to day 14 of life only in term infants. TNF-α, IL-6 and IL-8 levels were higher

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on day seven than on day 14 in both groups. Cortisol levels remained unchanged in preterm infants [71]. These changes in total and free tryptophan in the milk of preterm infants may affect their neurological development [71].

At birth (up to 60 hours after birth), 90% of tryptophan is in free form. The binding to albumin increases, and by the 5th day of life, only 40% of the tryptophan is in the free form [73] Only in 1979 did Tricklebank et al. report results on tryptophan binding to albumin in human plasma during the immediate postnatal period [74]. In the adult brain, serotonin does not cross the blood-brain barrier. However, in the neonatal period, there is a "membrane pump" responsible for the uptake of monoamines by endothelial cells and pericytes of central nervous system capillaries from birth [75]. At three weeks of age, the rat serotonergic system has biochemical markers of serotonin, 80% of those seen in adults [76]. It had already been seen that a diet low in tryptophan, such as one rich in corn, promotes behavioural changes, probably due to a serotonin-formation deficiency [77].

Tryptophan levels are high in newborns, and these levels decline slowly during the first postnatal week and then more slowly to reach adult levels by the end of the fourth week of life. During the first three weeks of life, the level of tryptophan is 2 to 4 times higher than that of an adult. Two neonatal peculiarities make this possible: 1) the lack of binding to serum albumin and 2) the greater capacity of synaptosomes to accumulate tryptophan [73]. In rodents, the brain shows a peak of tryptophan between 3 and 14 days of age [78]. An early study [79] of neonatal tryptophan metabolites observed three phases in urine samples: First, characterized by the absence of tryptophan metabolites from 1 to 14 days of life; Second, from 15 to 17 days of life, numerous conjugates of 3-hydroxykynurenine and kynurenine appear, and in 7 out of 10 cases, 3-hydroxyanthranilic acid (3AA) is present. The disappearance of all these metabolites characterized the third phase. This study concludes that there is a deficiency in the activity of the enzyme tryptophan peroxidase in the first days of life [79]. Concerning the melatonin metabolite, the milk, in neonatal urine and saliva samples, the circadian rhythm of melatonin expression was found to be set up after 12 weeks [80].

5. Genetics, Epigenetics and Tryptophan Metabolism

In tryptophan metabolism, neuroprotective or neurotoxic substances can be formed, which could decide whether the brain is healthy or sick in adult life. Depending on environmental information, it is an intricate mechanism of protection or aggression. If the organism is subjected to healthy guidance, the serotonin route will be chosen; if there is stress or inflammation, the chosen route is kynurenine, which can form excitotoxic quinolinic acid. Aggressive events in the first period of life have been linked to gene polymorphisms that induce schizophrenia. The DOHaD study considers how the period of development can be affected by genetic variations, such as polymorphisms, and how it can affect epigenetics with consequences for adult life.

Tryptophan metabolism may be associated with the production of neuroprotective or neurotoxic metabolites depending on the highlighted environmental factors. As neurotoxic agents, we have quinolinic acid, which can be genetically modified. Early life adversity has been associated with adult mood disorders [81–83]. The gene-environment relationship has been explored in the action of the serotonergic system on depression, with several studies reporting the polymorphisms of genes in this system associated with this mood disorder [84–87]. One landmark and widely cited study described the effect of early life adversity, moderated by the polymorphism of the serotonin transporter gene (5-HTT), in triggering the risk of depression [84]. However, in 2011, data from a 30-year longitudinal study with 13 measures of childhood adversity found no evidence to support the hypothesis of an association between the 5HTT polymorphism (5-HTTLPR) and mental disorders [85].

A study evaluated the hypothesis of an interaction between childhood physical abuse and the single nucleotide genetic polymorphism rs1360780, which participates in the control of the hypothalamic-pituitary-adrenal axis in the development of depression [88] reinforcing the importance of early events in adult depression. The results confirm the susceptibility of individuals with this polymorphism to the development of depression throughout life. The authors suggest that this polymorphism could be considered in the prevention of depression in individuals who were physically abused in childhood [88]. Polymorphisms in genes G protein-coupled receptor for 5-

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hydroxytryptamine 1 (HTR1A), serotonin-transporter-linked promoter region (5-HTTLPR), TPH2, of the active metabolite of tryptophan, serotonin, were analyzed concerning the severity of depressive symptoms induced by infection [89]. Polymorphism in the 5-HTTLPR gene was associated with increased depressive symptom severity and was also associated with decreased tryptophan concentrations. The data from this study may indicate that infection-induced depression may be a distinct type of depression [89]. A meta-analysis of 166 articles, including more than 30000 patients, examined 69 polymorphisms of the enzyme tryptophan hydroxylase2 that have been implicated in psychiatric disorders such as schizophrenia and suicidal ideation [90]. A meta-analysis had previously found an association between tryptophan hydroxylase polymorphism and schizophrenia and suicidal ideation. Previously, another meta-analysis had pointed to an association between tryptophan hydroxylase polymorphism and schizophrenia [91] and, which was highlighted 13 years later [92].

Early adversities in humans have also been related to these events. A study of 800 young Chinese using the Childhood Trauma Questionnaire, which assesses physical, emotional, and sexual abuse and emotional and physical neglect in early life, analyzed the interaction between gene (TPH2) and environment. The study found that the TPH2 gene polymorphism may play a role in early adversity, using magnetic resonance imaging to measure cortical volume. This affects anxiety behaviour, which is mediated by the volume of the cerebral grey matter of the right thalamus (right posterior parietal thalamus (RPPTha) and the parahippocampal gyrus [87]. In 2014, the first study linking early adversity with expression of genes for 5-HTT and TPH2 to depression was conducted and found that this interaction is associated with reduced synaptic serotonin and increased depressive symptoms [86]. The authors also point out that the 5-HTT and TPH2 polymorphism interaction is necessary for this result and not in isolation.

THP2 -/- mice survive to adulthood, but there is growth retardation and 50% lethality in the first four weeks of life. The animals showed growth retardation and altered autonomic control of sleep, feeding, thermoregulation, blood pressure and heart rate. In adulthood, they showed increased aggressive behaviour and maternal neglect [93]. Serotonin was associated with ethanol consumption and addiction [94]. Genetic deficiency of TPH2 in mice promotes increased ethanol consumption associated with an ethanol antidepressant phenotype (shorter immobility time in the forced swim test) [95]. Low tryptophan availability has been linked to alcohol dependence [94]. Low levels of tryptophan and so serotonin increase ethanol-induced impulsivity [96]. On the other hand, when lesions of serotoninergic fibres occur with bilateral ventricular injection of 5,7 dihydroxytryptamine (5,7-DHT) at three days of age in rats, these animals show a low preference for ethanol in adulthood [97]. These data contrast other studies in which 5,7-DHT was administered in adulthood, and higher ethanol consumption was observed [98]. These results confirm the relevance of manipulation during the period of vulnerability of the nervous system, promoting various processes of tissue adaptation to insults. In this context, it is known that mice without TPH2 are less anxious and show more social interaction, but social interaction shows elevated levels of aggression [99]. The first study to evaluate oxytocin levels in TPH -/- mice found increased oxytocin levels in the hypothalamus's prefrontal cortex and paraventricular nucleus [100]. Oxytocin in the prefrontal cortex reduces anxiety-like behaviour [101] and promotes social behaviour [102]. Given the range of polymorphisms or deletions of serotonin synthesis enzymes or serotonin itself, other pathways with phenotypic plasticity may arise to keep appropriate serotonin levels, such as reduction of serotonin catabolism [103], as well as modification of other systems such as oxytocin [100].

Protein transcription is the target of epigenetics, so we have epigenetically modular factors on the expression of enzymes that metabolize tryptophan. Epigenetics is the primary basis for phenotypic plasticity, and according to the DOHaD proposition, the phenotypic plasticity of development is the primary basis of the events that occur in this perinatal phase [104]. Epigenetics are the modifications to DNA which do not alter its sequence, such as DNA methylation, histone modifications, and non-coding RNA [105]. These modifications are promoted by environmental stimuli that affect phenotype. These epigenetic modifications can interact with each other, resulting in multiple layers of gene regulation. The environment and developmental changes can act on one or all these epigenetic influences. Epigenetic events can describe the relationship between early life

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events and adult pathologies' onset [104]. Few studies have linked the active metabolites of tryptophan to DNA. These studies have started recently, but they are mainly limited to the interference of serotonin in the action of histones and in mental and mental disorders.

Child abuse has been associated with a later risk for depression and anxiety disorders [82] as well as increased physiological reactivity in response to stress [106]. Child abuse was considered a risk factor for epigenetic change. The serotonin transporter gene (*SLC6A4* or *5HTT*) is of particular interest in the context of understanding the effects of child abuse. Several studies have found positive associations or trends between peripheral serotonin transporter gene (*SLC6A4*) promoter methylation and major depressive disorder (MDD) symptoms and childhood abuse [107]. It was found that methylation from SLC6A4 is associated with the report of abuse during childhood [108]. This result led to the exploration of the methylome in genes that may carry the risk of psychiatric disorders.

DNA methylation, genetic predisposition, and environmental exposures may predict disease risk [109]. An issue that is still controversial is individual resistance to antidepressants, which may lead to suicide risk. Variations in genes involved in serotonergic neurotransmission systems may interact with environmental factors to influence response to antidepressants [110,111]. Studies in a Chinese population evaluated polymorphisms in 10 serotonergic genes that interacted with early adversity and depression in adulthood and found that the TPH2 polymorphism was associated with antidepressant response related to early experiences [110]. A study of 300 depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) or non-SSRIs antidepressants evaluated TPH2 methylation in association with early adversity. It confirmed that this interaction can impair antidepressant response [112]. This study highlight the role of epigenetics in antidepressant response, which is fundamental to developing new drugs.

Accelerated tryptophan metabolism via IDO enzyme occurs in several disorders, such as neurodegeneration, cardiovascular diseases, infections and malignancies. Malignant cells can activate IDO enzyme expression [113] which is observed in many human cancers [114]. In tryptophan catabolism, the IDO enzyme has diverse biological roles in immune suppression and tumour progression [115]. In studies that do not involve the nervous system, a relationship between the activity of the IDO enzyme and tumour immune evasion in the breast was verified. This invasion was related to estrogen receptors (ER). Serum kynurenine levels, as well as tumour IDO enzyme expression, were lower in patients with estrogen-positive tumours. The IDO enzyme promoter is hypermethylated in ER-positive breast cancer. The association of ER overexpression with epigenetic downregulation of IDO enzyme appears to be a particular feature of breast cancer [116].

IDO enzyme inhibitors are an emerging class of drugs for cancer treatment. To date, there are several inhibitors available that have already entered clinical trials [115]. A recent meta-analysis indicates that IDO expression may be a prognostic marker of cancer in various tissues and that its expression is a promising pharmaceutical target [113].

Serotonin, independent of its action as a neurotransmitter, is directly involved in epigenetic modifications in mediating gene expression [117]. This epigenetic role of serotonin has been called "H3 serotonylation" [118]. In it, serotonin can be covalently attached to histone H3, residue Q5 of histone 3, to regulate the transcription process [119]. Histone 3 glutamine 5 (H3Q5) is the main serotonylation site, and this co-occurs with trimethylated H3 lysine 4 (H3K4me3), which is related to active transcription [117]. Other neurotransmitters can be substrates for modifying chromatin [120].

Chronic social stress promotes transcriptional changes in the dorsal raphe nucleus, the main center of serotoninergic projection neurons in the CNS. These changes are associated with mood disorders such as depression, results observed in animal models and in post-mortem tissues of depressed individuals [121]. Histone H3 serotonylation patterns are reorganized in response to chronic stress they observed that reducing H3 serotonylation levels in the raphe nuclei before chronic stress reverses stress-mediated gene expression, which leads to depression [121].

Neonatal stress promotes greater susceptibility to chronic social stress in adulthood, which appears to be mediated by the nucleus accumbens [122]. Neonatal stress promotes long-lasting changes in histone modifications in the nucleus accumbens [123], increasing the risk for depression and stress in adulthood [124]. It has been shown that there is involvement at the transcriptional or

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physiological levels in the nucleus accumbens in this process; the dimethylation of lysine 79 of histone H3 (H3K79me2) seems to be the target [123]. It is suggested that the inhibitor of H3K79me2 deposition can reverse the behavioural deficits induced by stress in early life [123]. This study is a pioneer in exploring drugs in neuropsychiatric disease models. They administered an inhibitor that reduces H3K79 methylation and showed that it reversed the effects of stress in early life [123].

Serotonylation of histones occurs in the placenta, showing an intersection between placental serotonin and chromatin [125]. Histone alterations in the placenta can influence the transcriptome of the embryo's brain, potentially affecting behaviour or disease risk in adulthood [125]. Studies into the incorporation of serotonin into epigenetic factors are still in their infancy. Important discoveries could solve several gaps in neurotransmission, early adversity, and the availability of neurotransmitter precursors.

The relationship between serotonin in early life and adult outcomes may play a significant role in Down syndrome, a genetic disorder characterized by the triplication of chromosome 21. Intellectual disability is one of the significant features of this disorder, and the individual usually has a mental age of eight years. Intellectual deficits are associated with alterations in brain development, such as impaired neurogenesis, reduced number of hippocampal neurons, reduced density of granular cells in the cerebellum, astrocytic hypertrophy, prominent microglia, and impaired myelination. These changes may be reminiscent of fetal life [126]. A study in mice with trisomy 21 has shown that treatment with SSRIs (fluoxetine, 5 mg/kg) during lactation restores neurodevelopmental alterations that persist into adulthood [127]. The authors suggest the relevant role of serotonin in developing the nervous system in this process and suggest prompt treatment with SSRI (fluoxetine) as a new hope for treating the syndrome.

6. DOHaD—Early and Late Roles of Tryptophan Metabolites in Neurodevelopment

The Serotonin Pathway

When expressed in excess or deficiency during early life, perinatal or childhood, the bioactive metabolites of tryptophan are associated with modulation of neurodevelopment with lasting repercussions for health or disease throughout life. We will present studies that characterize this statement with the involvement of the primary bioactive metabolites of tryptophan. Under stress or inflammation, tryptophan is metabolized into neurotoxic or neuroprotective substances.

Tryptophan metabolism has two pathways: a) the serotonin/melatonin pathway necessary to maintain well-being and biological rhythm. Changes in their homeostatic concentrations can lead to pathologies such as depression and sleep disorders; b) the kynurenine pathway that will form TRYCATS. Like serotonin, TRYCATS may be targets of early environmental influences as they participate in mental disorders and neurodegenerative diseases later in life. Increased kynurenic acid is associated with schizophrenia [31], while elevated levels of quinolinic acid are associated with such as Alzheimer's, Parkinson's, and Huntington's [128,129]. Anxiogenic and anxiolytic TRYCATs were also classified [130].

In the development of the nervous system, serotonin is one of the first neurotransmitters to appear [131,132]. In the 1960s, researchers found that serotonin deficiency in neonates and during the first few months of life due to excessive amounts of phenylalanine and tyrosine resulted in reduced learning ability that continued into adulthood [133] and this result is reversed with administration of melatonin or 5-hydroxytryptophan [134].

The relationship between serotonin activity in adulthood and early adversity was analyzed. A study analyzed serotonin synthesis using positron emission tomography with the tracer alpha(11C) methyl-L-tryptophan, which is an index of serotonin synthesis capacity, in 27-year-old men who attended schools in disadvantaged areas and had been subjected to high levels of physical aggression during childhood and adolescence (6, 10-15 years) [135]. They found lower serotonin synthesis in the bilateral orbitofrontal cortex in these individuals in adulthood compared to individuals who had not experienced physical aggression. No changes were seen in the free tryptophan levels or the enzyme TPH2 [135]. The authors suggest that the low levels of serotonin in individuals who experienced early

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aggression may function as a vulnerability trait and that other protective traits may have helped to control aggressive impulses. The unchanged levels of tryptophan may indicate that due to perinatal stress, there was epigenetic marking for the kynurenine pathway, formation of kynurenic acid, and perpetuation of the deviation of the pathways due to early stress. Using the same technique as in the earlier study, the researchers found that in young people with a mean age of 27 years, childhood adversities were linked to decreased serotonin synthesis in brain regions involved in emotion regulation. In the case of smoking during pregnancy or low birth weight, a reduction in serotonin synthesis was seen in the medial orbitofrontal cortex. In complicated births, especially those in which the fetus showed physiological stress, lower serotonin synthesis was also seen in the hippocampus [136].

During the preliminary period of life, molecules that constitute serotonergic neurotransmission can be targets of drugs to treat pathologies that involve dysfunction of this neurotransmitter. However, the action of these drugs can generate changes in this intracellular tryptophan metabolism, with permanent and even transgenerational consequences. During this period of life, the use of drugs (SSRI) that target, for example, the selective serotonin reuptake protein (SERT), can promote permanent molecular changes. We need to point out that SERT is present not only in the nervous system but also in the bloodstream within platelets [137]. The SSRI acting on platelets regulates the concentration of free serotonin in plasma. Thus, in addition to their role in the nervous system, SSRIs can modulate serotonin signalling throughout the body [138].

During pregnancy, SSRIs can affect the fetoplacental unit on the plaques, promoting an increase in placental vascular resistance or compromising blood perfusion in the fetoplacental unit [139]. Modular SSRIs have serotonin availability through organic cation transporter 3 (OCT3) in the placenta. A study demonstrated that SSRI increases serotonin in the fetus by inhibiting SERT and OCT3 [139]. It is known that a significant percentage of pregnant women and postpartum mothers are treated with SSRIs [140], exposing fetuses or neonates to elevated levels of serotonin during a critical period of nervous system development.

In rodents, it has been found that an SSRI (paroxetine) reduced DNA methyltransferase mRNA expression in the hippocampus during the second and third weeks of life [141]. In addition, using SSRIs during pregnancy has been associated with increased brain function using magnetic resonance imaging and increased activation of several higher regions involved in sensory processing or memory integration in adult offspring [142]. A recent review has highlighted the effects of SSRIs during human pregnancy on neonatal morbidity and preterm birth [143]. In all species studied, the increase in maternal serotonin caused by SSRI promotes a decrease in uterine-placental vascular perfusion, which reduces blood flow to the uterus, placenta, and fetus. This results in an increased risk of low birth weight and premature birth associated with neonatal morbidity [143].

The use of selective SSRIs to increase perinatal serotonin levels for the treatment of depression in pregnant or lactating women has been controversial in the literature because of evidence of adverse effects on the fetus and neonate. Early studies report that the use of SSRIs in pregnant women in the first [144] or third [145] trimester of pregnancy does not result in significant postnatal complications. On the other hand, a literature review published in the early 2000s found no evidence of impairment to the newborn of SSRIs ingested by the mother at the end of pregnancy or breastfeeding [146]. These authors cautioned professionals that there was a lack of data upon which treatment decisions could be based [146]. However, a review published a decade later shows that SSRIs may promote congenital malformations when administered in the third trimester of pregnancy [147]. In this review, cardiac defects in the newborn were proved with the use of paroxetine by the pregnant woman. Experimental studies in rodents treated with SSRIs during pregnancy may alter the emotional behaviour of the offspring in adulthood, leading to depression [141].

To analyze in detail the effect of high serotonin levels on postnatal development, a group of researchers began studies promoting the enhancement of brain serotonin levels through the administration of SSRIs during the lactation period. In the first study, it was found that treatment with an SSRI (citalopram) during lactation reduced the aggressive behaviour of rats in adulthood [148]. These results showed the role of high serotonin levels during the critical development period of the nervous system on behavioural expression in adulthood. The use of another SSRI (fluoxetine)

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during lactation has been shown to reduce depressive-like behaviour in rats in adulthood [149]. Administration of SSRIs during the neonatal period has been shown to alter development and growth in rats [150–154]. Later, the same research group found a reduction in the area of the neuronal body and the number of serotoninergic neurons in the raphe nuclei in adulthood with SSRI in neonatal life [155]. These animals showed reduced body weight and accumulation of white adipose tissue, with increased expression of the 5HT2C receptor and reduced NPY gene expression in the hypothalamus [156] (Figure 2).

In humans, it has been seen that children exposed to SSRIs during pregnancy may show deficits in psychomotor development [157] and altered responses to stress [158]. Studies on the effects of SSRIs during early periods in humans are controversial and difficult to isolate. One study associated anatomical data from brain structures, such as the surface of the parietal lobe, with depressive symptoms in middle childhood. They found that structural changes with SSRI treatment are only slightly related to depression [159].

Several systematic reviews with meta-analysis have been conducted in recent years, with the use of SSRI during pregnancy or lactation with mental disorders, particularly autism, after, but all report inconsistency in the data to make a direct association [160–164]. More comprehensive studies are needed on different SSRIs; most studies focus on specific mechanisms of SSRI action during pregnancy. Understanding the action of SSRIs, promoting changes during fetal or early neonatal development, is essential to optimize strategies for the treatment of psychiatric disorders during pregnancy or lactation.

7. Kynurenine Pathway

Concerning the kynurenine pathway, several studies have linked this pathway during fetal or neonatal life to molecular changes in nervous system function in adulthood. The kynurenine pathway appears to be associated with neurodevelopmental disorders [31,165,166]. Alterations in kynurenine are associated with psychiatric disorders such as schizophrenia and depression [167,168]. It has been discussed that in psychiatric disorders, tryptophan catabolism is favoured over the kynurenine pathway [169]. The developmental hypothesis of schizophrenia is based on environmental risk factors acting before, during, and after birth [170]. The aetiology of this disease is a combination of genetic factors and environmental exposures, such as stress and infection during critical periods of development [171].

Maternal immune activation is a model of neurodevelopmental disorder with long-term effects [172]. Epidemiologic data suggest that approximately 45% of schizophrenia cases are associated with prenatal infection [173]. Induction of maternal immune response with poly I: C (a viral complex that activates tryptophan metabolism in the kynurenine pathway to compounds that can modulate the activity of glutamatergic receptors) leads to reduced cognition, sensorimotor deficits, anxious behaviour, increased amphetamine-induced behaviour, and increased dopamine turnover in adults, behaviours characteristic of schizophrenia [174] (Figure 3). Rats treated with l-kynurenine in neonatal life show reduced sensorimotor and working memory, conditioned fear in adulthood, and elevated brain levels of kynurenic acid in neonatal life [175]. In several animal models of maternal immune infection, exposure to poly: C promotes differentiated neuropathological behavioural phenotypes in the offspring, depending on the stage of pregnancy at which they are inoculated. Adult mice exposed at midgestational showed a reduction in exploratory behaviour, while those exposed at late gestation showed an increase in this behaviour [176]. Exposure at the end of gestation caused increased apoptosis in the hippocampal dentate gyrus and increased cytokines in the brain in adulthood. The timing of the stimulus has different effects that persist into adulthood [176].

The main action of kynurenic acid is the antagonism of glutamate. In schizophrenia, there is an increase in kynurenic acid in the brain, which leads to excessive blockade of glutamatergic receptors (N-methyl-D-aspartate- NMDA) and manages the psychotic symptoms and cognitive deficits of the disease [177]. In addition to this action, kynurenic acid also antagonizes α-7 nicotinic receptors [178], which is associated with cognitive impairment, a critical point in schizophrenia that precedes all other

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symptoms [178] Glutamate receptors participate in normal brain development, acting on neural structure, connectivity, and synaptic plasticity of the neonatal brain [179].

One experimental strategy to drive the kynurenine pathway toward kynurenic acid production is to inhibit the kynurenine-3-monooxygenase enzyme (KMO) [180]. This inhibition during gestation can cause changes in protein expression, neurogenesis, neuronal structure, and synaptic transmission in the hippocampus [168]. During pregnancy, KMO inhibition promoted different changes in the neocortex and hippocampus in rodents [181]. The expression of GluN2A (NMDA receptor subunit) in the neocortex was increased, and the hippocampus was decreased. This increase may be related to the accelerated development of cortical regions but delayed formation of hippocampal circuitry [181]. This protein engages in dendrite formation and fear-learning responses in the amygdala and fear memory in the prefrontal cortex [182–184]. Higher GluN2A expression in the prefrontal cortex may show increased resistance to neurogenerative lesions, while in the hippocampus, it may show greater susceptibility to these lesions [181]. In the cerebellum, a reduction in the expression of the unco-ordinated-5H3 (unc5H3) protein has been seen, associated with gross abnormalities in cerebellar morphology and motor control [185]. This protein has also been upregulated in the brainstem, where it has been implicated in the maturation of dopaminergic projections and the efficiency of their transmission. Another altered protein is Disrupted-in-Schizophrenia (DISC1), which was increased in the neocortex and decreased in the cerebellum. It may be possible that the elevated levels of kynurenic acid altered these proteins; thus, associating the kynurenine metabolism plays a critical role in early embryonic brain development [181]. Still, with the manipulation of kynurenic acid administered in adolescent animals, social behaviour was impaired. However, there was no such effect when it was administrated to an adult animal. These results show that by acting on the antagonism of NMDA and α-7 ACh receptors during nervous system development, kynurenic acid may cause long-term social damage by acting on phenotypic plasticity [186]. On the other hand, researchers have shown that increased levels of kynurenic acid during adolescence do not alter hippocampal-dependent memory behaviour [187].

When there is early exposure to a kynurenine precursor during pregnancy and lactation (GD15 and PD21) results in elevated kynurenic acid in the prefrontal cortex that persists into adulthood, with deficits in learning and attention in adulthood [188]. Increase of brain kynurenic acid in rats, through dietary exposure to its precursor kynurenine from embryonic day 15 to postnatal day 21, found high levels of kynurenic acid, 500% higher than controls, in the forebrain on the last day of fetal life. The elevated levels persisted into adulthood, 75% higher than the control, and were associated with changes in several excitability markers in the prefrontal cortex, such as the expression of the nicotinic acetylcholine receptor alpha α7nAChR and the AMPA receptor subunit (mGluR2), which were reduced by approximately 20% [67]. A decade ago, an experimental model of schizophrenia with elevated kynurenic acid during early development was proposed [189].

Malnutrition is another early life event associated with neurodevelopmental disorders [190]. Perinatal malnutrition alters the two significant pathways of tryptophan metabolism. Initial studies have shown that perinatal malnutrition promotes an increase in serotonin levels in rat pups [191,192] and induces selective and persistent changes in the cerebral metabolism of kynurenine, increasing the concentrations of the metabolite's kynurenine and xanthunic acid in the adult brain [193].

The kynurenine pathway plays a role in the immune response to inflammation [194]. In the brain, the products of this pathway have neuroprotective or neurotoxic properties or immunomodulatory effects [29]. The kynurenine pathway has recently been implicated in neurodevelopmental disorders such as autism [195]. Although studies have shown alterations in tryptophan metabolism enzymes [196] or their metabolites [197,198]. Individuals with autism may have several metabolic abnormalities, including those related to tryptophan metabolism, as identified by urine metabolomics studies [199]. A preferential formation of xanthurenic acid and quinolinic acid in the metabolism of tryptophan, with a concomitant reduction in the formation of quinurenic acid, was found in a study of 30 children with autism aged three to seven years. A study, this time involving 68 children with autism, found higher levels of the enzyme 3-hydroxykynurenine and kynurenic acid in these children than in controls despite no differences in serum tryptophan levels

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[195]. However, in autism disorder, a recent systematic review with meta-analysis, including 25 articles with 3557 patients with autism spectrum disorder, revealed that there is no evidence for abnormalities in tryptophan metabolism in the pathophysiological disorder of autism [200].

The existence of tryptophan metabolism biomarkers for diagnosing neurological disorders, especially neurodevelopmental disorders, is currently.

8. Final Considerations

Tryptophan is metabolized into bioactive substances that are key to good body function, such as serotonin, kynurenine, and melatonin. The enzymes that participate in this process are key elements and are often the target of early genetic and epigenetic modifications that last throughout life. The mechanisms by which the activation of one enzyme over another is modulated are still unclear. In the nervous system, here is evidence from the observation of tryptophan metabolism in early life with the existence of neurodevelopmental and neurodegenerative diseases. Tryptophan metabolism is shaped by environmental influences early in life and present in organic functioning that persists into adulthood, and may be related to disorders, particularly in the functioning of the nervous system.

Tryptophan is metabolized into bioactive substances that are essential for the proper functioning of the body, such as serotonin, kynurenine, and melatonin. The enzymes involved in this process are essential elements and are often the target of early genetic and epigenetic modifications that persist throughout life. The mechanisms by which one enzyme is activated to the detriment of another are still unclear. In the nervous system, the observation of tryptophan metabolism in early life and the existence of neurodevelopmental and neurodegenerative diseases are evident. Tryptophan metabolism is shaped by environmental influences early in life. It is present in organ functions that persist into adulthood and may be associated with disorders, particularly in the functioning of the nervous system.

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