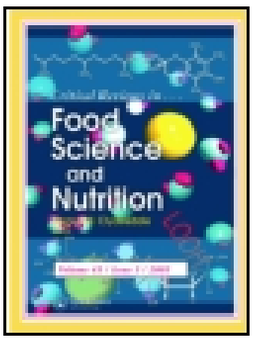

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How important is tryptophan in human health?

Joanna Kałużna-Czaplińska[1], Paulina Gątarek[1], Salvatore Chirumbolo[2], Max Stanley Chartrand[3], Geir Bjørklund[4]

[1]Department of Chemistry, Institute of General and Ecological Chemistry, Lodz University of Technology, Lodz, Poland

[2]Department of Neurological and Movement Sciences, University of Verona, Italy

[3]DigiCare Behavioral Research, Casa Grande, AZ, USA

[4]Council for Nutritional and Environmental Medicine, Mo i Rana, Norway

Corresponding author: Joanna Kałużna-Czaplińska, Department of Chemistry, Institute of General and Ecological Chemistry, Lodz University of Technology, Zeromskiego 116, 90--924 Lodz, Poland, Phone: +48 426313091, Fax: +48 426313128, E-mail: joanna.kaluzna-czaplinska@p.lodz.pl

Abstract

Tryptophan (Trp) is an amino acid and an essential component of the human diet. It plays a crucial role in many metabolic functions. Clinicians can use Trp levels in the course of diagnosing various metabolic disorders and the symptoms associated with those diseases. Furthermore, supplementation with this amino acid is considered in the treatment of depression and sleep disorders, mainly due to the Trp relationship with the synthesis of serotonin (5-HT) and melatonin. It is also used in helping to resolve cognitive disorders, anxiety, or neurodegenerative diseases. Reduced secretion of serotonin is associated with autism spectrum disorder, obesity, anorexia and bulimia nervosa, and other diseases presenting peripherals symptoms. The literature strongly suggests that Trp has a significant role in the correct

functionality of the brain-gut axis and immunology. This information leads to the consideration of Trp as an essential dietary component due to its role in the serotonin pathway. A reduced availability of Trp in diet and nutraceutical supplementation should be considered with greater concern than one might expect. This paper constitutes a review of the more salient aspects gleaned from the current knowledge base about the role of Trp in diseases, associated nutritional disorders, and food science, in general.

Keywords

tryptophan; serotonin; metabolic disorder; neurodegenerative disease; food technology; human diet

Introduction

The role of the essential amino acid tryptophan (Trp) is gaining in interest relative to dietary and nutritional sciences. Recent research has demonstrated that this amino acid exerts a protective action in the intestine, as it contributes to the enhanced expression of the tight junction proteins claudin-3 and *zonula occludens* (ZO-1) in the jejunum of experimental animals (Liu et al., 2017). Its fundamental importance appears mostly in its relationship with serotonin, which is important in food-to-nutrition synthesis. Past research has suggested a direct connection between serotonin production and the available circulating Trp, recently proposed as a hallmark as a possible marker of psychiatric serotonin-related disorders (Comai et al., 2016). From a food technology viewpoint, the importance of Trp in human physiology would suggest recommendations and guidelines by worldwide experts to supplement or enrich foods with Trp. Due to the complexity of the relationship of serotonin and melatonin and circadian rhythms, it's hard to ascertain or attribute the needed levels of Trp in a given diet (Hulsken et al., 2013; Silva et al., 2017).

However, several researchers have suggested that Trp supplementation in a daily diet might improve pharmacotherapy in some diseases **(Figure 1).** Because of the tryptophan has comparatively low tissue storage and their concentration in the body is low, compared to other amino acids, for healthy nutrition are needed only small amounts (Richard et al., 2009). Some food products containing tryptophan are presented in **Table 1** (Rambali et al., 2002; Richard et al., 2009; USDA Food Composition Databases, 2017). The recommended daily dose for adults is estimated to be between 250 mg and 425 mg, which results in a dietary intake of 3.5 to 6.0 mg/kg of body weight per day (Richard et al., 2009).

Tryptophan is an essential component of the diet. It plays a key role in protein synthesis, and is a precursor of biologically active compounds such as serotonin, melatonin, quinolinic acid, kynurenic acid, tryptamine, and also coenzymes important for electron transfer reaction (redox balance of metabolism), such as nicotinamide adenine dinucleotide (NAD+). This compound, which are final product tryptophan metabolism, might be produced from ingested tryptophan but also vitamin B3 (niacin) (Richard et al., 2009; de Figueiredo et al., 2011; Palego et al., 2016). To people health is detrimental both deficiency and excessive intake. Tryptophan has been used to treat variety disorders, but in most countries has been withdrawn. During the treatment of tryptophan preparations have been observed undesirable symptoms including a variety of pulmonary, cutaneous, and neurologic symptoms, and also eosinophilia-myalgia syndrome, and disease associated with muscle pain. Many different diseases and disorders have been linked with tryptophan and its metabolites. An increased metabolism of Trp, or adverse effects of low Trp such as decreased absorption or intake, have been observed in different types of pathology. It should be mention disease and disorders such as premenstrual syndrome (PMS) (tryptophan plays a role in increased activation of Trp catabolism), pellagra (caused by a deficiency of niacin which precursor is Trp), chronic kidney disease (is observed alterations in Trp metabolism in the case of kynurenine pathway (Karu et al., 2016), coeliac disease (availability of Trp to the brain is low, especially in subjects with depression), Parkinson's disease (large neutral amino acid compete with Trp), mental disorders (reduced availability of Trp what is consequence is low level of serotonin) (Sainio E. L., Pulkki K. and Young S. N., 1996; Russo et al., 2009), sleep disorders (abnormal level of melatonin, which is synthesize from serotonin) (Kaczor and Skalski,

2016), schizophrenia (dysfunctional serotonin transmission), bulimia and anorexia (depletion of Trp) (Sainio E. L., Pulkki K. and Young S. N., 1996; Russo et al., 2009).

It is well known that Trp is only available through the dietary process, as its precursors allow gut microflora to synthesize the essential amino acid in humans. Tryptophan can be metabolized through the methoxyindole and kynurenine pathways. The kynurenine pathway, which takes up about 95% of the biologically available Trp, is controlled by the rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO) and Trp 2,3-dioxygenase (TDO).

Stress hormones and Trp induce TDO synthesis and activation, while IDO can be induced by pro-inflammatory, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and Th-1 type cytokines, i.e. during an innate response of the immune system. IDO suppresses the activity causing the induction of TDO, and vice versa, while the ratio of kynurenine (products) to Trp (substrate) gives information about IDO activity. Upregulation of the IDO activity caused by chronic inflammation of the immune system could be a major factor in the initiation and propagation of obesity and associated metabolic syndrome (Mangge et al., 2014).

Tryptophan supplementation could promote synthesis and neurotransmission of serotonin. Moreover, it may be effective in treating disorders of serotonin deficiency by increasing the precursor for 5-HT synthesis and normalizing its release (Haleem, 2012). Levels of Trp, and hence its circulating bioavailability, does not seem to be directly linked to cognition and mood improvements, as recent reports suggest that excess of Trp impairs cognition, rather than improving it (Hulsken et al., 2013). On the other side, a deficiency in Trp, caused by malnutrition, may affect the central and peripheral serotoninergic pathways, although further

nutrition-derived hormonal molecules may rescue some of this deficiency (Patrick and Arnes, 2014).

With serotonergic dysfunction have been associated with symptoms of panic, depression, aggression and suicidality. Because the serotonin system is involved in the various psychiatric disorders, but not only, serotonin system is also involved in the regulation of satiety, it can be concluded that the activity of serotonin can be important in the pathophysiology of eating disorders such as anorexia nervosa. A fundamental concern for nutritionists and food technologists is to focus on the role of Trp in neurological and immune disorders, to achieve a deep awareness and knowledge of the risks and potentials associated with the supplementation use of this amino acid. The aim of this paper is based on the currently existing and very recent literature to present a more focused viewpoint relative to the role of Trp in diseases associated with human nutritional disorders.

1. Tryptophan and irritable bowel syndrome

One of the most common alimentary tract illnesses in humans is irritable bowel syndrome (IBS). This disease also constitutes a significant social problem. IBS is a bowel function disorder. Pain associated with defecation and defecation frequency or stool consistency characterizes this disease. Still unclear is etiopathology of the illness. Pathological factors include, among others, disturbances in the functions of serotonin at this level of the digestive process (Żelowski et al., 2013). IBS is a functional gastrointestinal disease, because these disorders arise from dysfunction of the organ, excluding morphological changes within it (Fitzgerald et al., 2008).

There are four clinical forms of this syndrome: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M) and unsubtyped IBS (Longstreth et al., 2006). Throughout the

world, about 10--20% of adolescents and adults exhibit symptoms associated with IBS (Fitzgerald et al., 2008). Irritable bowel syndrome is more common in women than in men. The disease develops most often in the third decade of life (Drossman et al., 2002). The factors causing this disease include, among others, environmental, genetic, depression, inflammatory predispositions, and chronic stress (Fitzgerald et al., 2008; Żelowski et al., 2013).

Fitzgerald et al. (2008) examined patients with IBS and healthy, of comparable age and body mass index (BMI) and sex-matched controls. They observed the higher concentration of kynurenine in the blood of patients with IBS in comparison with the control group and positive correlation between the kynurenine/tryptophan (Kyn/Trp) ratio and IBS symptom severity (Fitzgerald et al., 2008).

Keszthelyi et al. (2012) demonstrated a relationship between the amount of serotonin, synthesized in the brain, and the amount of Trp supplied to the body with diet. Their randomized placebo-controlled study suggested that the sudden shortage of the precursor of serotonin obtained by administering an amino acid-enriched beverage lacking Trp to patients resulted in the dramatic reduction of the concentration of serotonin in the blood, as well as, a decrease in the level of 5-hydroxyindoleacetic acid in urine. In contrast, there was no change in the concentration of these compounds in the intestinal mucosa. The researchers concluded that that 5-HT synthesis in the brain is highly dependent on the availability of Trp in plasma, which is influenced by the competitive uptake of other large neutral amino acids (LNAAs) and Trp across the blood-brain barrier (Kaszthelyi, 2012).

Other scientists measured serum serotonin concentration in individuals with irritable bowel syndrome, compared with control group, and also evaluated the urine concentration of 5-

hydroxyindole acetic acid (5-HIAA), which is a metabolite of serotonin. They examined participants aged 19--50 years, including healthy subjects, patients with predominant constipation (IBS-C) and patients with predominant diarrhea (IBS-D). The results pointed to a reduction of serotonin concentration in patients with IBS-C and IBS-D. In all patients with IBS, a decrease in urinary excretion of 5-hydroxyindole acetic acid was observed. These results indicate that disturbed metabolism of serotonin could play a role in the pathogenesis of functional bowel diseases (Moskwa et al., 2007).

Studies conducted by Atkinson et al. (2006), showed that patients with IBS-D (aged 19--52 years) have a higher concentration of serotonin in the blood than healthy patients, both in the fasting and during the postprandial time. However, the differences were not detected as IBS with constipation (IBS-C, aged 19--52 years). Food intake significantly increased levels of serotonin in the blood of patients with IBS with diarrhea, with respect to healthy subjects (n = 35, aged 18--46 years). The results assessed the concept that an impaired release might characterize C-IBS, whereas D-IBS is characterized by reduced serotonin reuptake (Atkinson et al., 2006).

Reports by Dunlop et al. (2005) indicated an increase in the postprandial levels of serotonin in the blood of patients with a diarrhea form of IBS (IBS-D) and a significant reduction in patients with constipation-predominant IBS (IBS-C), compared to healthy controls (Dunlop et al., 2005). Dunlop et al. (2005) examined 15 patients with IBS-D, 15 patients with IBS-C and 15 healthy control participants. This study compared postprandial serotonin release and mucosal serotonin metabolism in various types of IBS. The results demonstrated that patients with IBS-C showed impaired postprandial serotonin release.

Houghton et al. (2003) examined 39 female patients with IBS-D aged 19--52 years, and 20 healthy females aged 20--46 years. Obtained data suggested that postprandial symptomatology could be connected with increased plasma serotonin concentration in IBS-D patients (Houghton et al., 2003; Dunlop et al., 2005). Furthermore, sleep disorders are frequently associated with women affected by IBS. In this circumstance, it has been observed that a reduction in the early nighttime ratio of melatonin: Trp may be related to the altered sleep status in IBS cases (Heitkemper et al., 2016).

Current therapy of IBS should involve Trp biology and metabolism, either by improving diet panels, herbal therapy and/or using pharmacotherapeutic drugs able to prevent or reduce Trp catabolism and chemical degradation (Grundmann et al., 2010; Catanzaro et al., 2014; Shi et al., 2015). At the same time, the controversial role of the excess of Trp that has been reported in past studies on gut mucosa cannot yet be dismissed (Madara and Carlsso, 1991).

2. Obesity, overweight and tryptophan metabolism

In the last four decades, obesity has increased dramatically throughout the world. In 1980 the number of obese and overweight people were 857 million, whereas by 2013 this number had increased to 2.1 billion (Youssef, 2015). Obesity is a very complex, multifactorial metabolic disorder, which is often related to an immune-mediated systemic inflammation of the adipose tissue and to insulin resistance and hyperlipoproteinemia, where a major role is exerted by NF-κB (Catrysse and Van Loo, 2017). The basic determinants of obesity can be both over-nutrition and lack of physical exercise. Simple reasoning on a diet should suggest that the excessive intake of food might even lead to an excess intake of Trp precursors and of food-derived Trp.

Furthermore, Trp is responsible for the calorie intake regulation (Mangge et al., 2014). Recent data suggests that obesity is associated with altered Trp and tyrosine (Tyr) metabolism (Strasser et al., 2015). As previously reported, these compounds also play a role in neuropsychiatric symptoms (Andrè et al., 2014). As the primary pathway of Trp metabolism is the kynurenine pathway, and indoleamine-2,3-dioxygenase (IDO) is the first enzyme of the pathway, these proinflammatory molecules that stimulate IDO may cause or exacerbate obesity (Andrè et al., 2014; Mangge et al., 2014; Strasser et al., 2015). Yet, apparently contradictory issues do exist, particularly regarding activity of Trp based on its circulating levels in obese subjects, or in those circumstances where metabolic syndrome may have consequences in other anatomic regions of the human body (Oxenkrug, 2013; Mangge et al., 2014; Oxenkrug, 2015; Yu et al., 2017).

In overweight adults, Strasser et al. (2015) investigated the effect of a two-week caloric restriction weight loss diet (CRWLD) on the circulating levels of leptin, on further inflammatory biomarkers and Assessing the short-term dietary effects of Trp and inflammatory biomarkers in overweight adults (Strasser et al., 2015), researchers found an impairment in the biosynthesis of serotonin from its natural precursor. This may be related to the increased susceptibility for mood disorders and carbohydrate craving observed in the study. Leptin is a hormonal peptide, produced by adipocytes, which is correlated to body fat homeostasis and satiety, as it contributes in regulating food intake and energy balance but the functionality of which is also strongly associated with the neurological activity (Zhou et al., 1997; Van Doorn et al., 2017). High levels of leptin characterize most of the patients with obesity (Lönnqvist et al., 1995; Hundal et al., 2000; Savino et al., 2013), suggesting the involvement of a peripheral and central resistance. Recent papers showed that a reduction of body weight has a dramatic impact on the circulating

levels of leptin (Klempel and Varady, 2011; Musil et al., 2015). In the research carried on by Strasser et al. (2015), the reduction of leptin concentrations in the circulation can improve insulin sensitivity, blood pressure, and blood lipid levels. Concentrations of Trp and Kyn decreased significantly by 15 and 17% for the low caloric diet (LCD) group and by 21 and 16% for the very low-calorie diet (VLCD) group, while leptin was reduced by 46% (Strasser et al., 2015).

Reducing body weight by increasing metabolic activity and accelerating the onset of satiety may involve a serotoninergic-driven mechanism. For this reason, it might be very useful in the treatment of obesity to consider the supplementation of Trp during caloric restriction diet (Yu et al., 2017). Also, increased availability of Trp can increase the production of serotonin and reduce the symptoms of depression in people struggling with overweight (Oh et al., 2016). Thus, Trp supplementation could prove very useful in the treatment of uncontrolled weight gain or prevent neuropsychiatric symptoms (Strasser et al., 2015).

Despite the fact that weight loss in obese patients showed an improvement or prevention of changes in the ratio of the intake/bioavailable Trp and other signals related to obesity that activates the immune system and inflammation, in obese patients with bariatric surgical intervention a reduction in this ratio or of immune markers was not found (Brandacher et al., 2007). Current literature reports several studies dealing with obesity and Trp metabolism, which are often related to immune-mediated inflammation, with notorious differences between juveniles and adults (Mangge et al., 2014; Reininghaus et al., 2014; Raheya et al., 2015).

In a study from a group with Mangee et al. (2014), 527 participants aged between 10--65 years were analyzed. Results showed that Kyn serum levels and Kyn/Trp ratio to overweight/obese adults (age from 18, to 65 years), significantly increased in comparison to controls. Data for

ow/ob juvenile males (age ≤18 years) showed decreased Kyn/Trp ratio values compared to controls. Furthermore, juveniles fulfilling the criteria of the metabolic syndrome exhibited constant Kyn/Trp ratio and Kyn, whereas adults with MetS had significantly increased Kyn and Kyn/Trp ratio. Trp serum levels decreased in adult ow/ob females but were not markedly different from normal weighted patients in the ow/ob groups or between ow/ob group with or without MetS (Mangge et al., 2014).

The results from these researchers suggested that Trp metabolism and obesity vary significantly between juveniles and adults. This indicates that early onset low-grade inflammation, which can be found in obese adolescents, is different from adults, and that juveniles are more likely to suffer from a process driven by a Th2-mediated response, contrarily to obese adults, where a Th1 immune mechanism is prevalent. These facts have potential clinical significance, because, first, conservative treatment of obesity through lifestyle changes include more prevalent physical activity during childhood and adolescence, and can prevent the critical transition to more aggressive immunology before there is irreversible clinical damage. Second, a simple analytical determination of the concentration of Kyn/Trp may provide more reliable diagnostic evidence of the presence of Th-1 proinflammatory markers regardless of age, particularly in obese patients (Mangge et al., 2014).

Furthermore, scientists have indicated that potential pathogenic links do exist between serotonin levels, chronic immune activation and in decreased IDO-mediated Trp in obesity (Ritze et al., 2015; Ritze et al., 2016). Immune activation and systemic inflammation are associated with obesity comorbidity, while at the same time it is connected with synthesized and released proinflammatory cytokines (like TNF-α, INF-γ, hormones- leptin and others) in adipose tissue.

IDO is inducible by IFN-γ; and is also involved in the regulation of immune responses and degraded Trp to form N-formyl kynurenine, which subsequently can convert to niacin. Furthermore, IDO can reduce Trp plasma levels in morbidly obese patients. Serotonin production may be reduced by Trp metabolic changes, and this can in turn contribute to depression, mood disturbances, and impaired satiety leading to increased caloric uptake and finally obesity.

Obesity has shown to be associated with a reduced concentration of Trp in the plasma, independently from dietary intake or weight reduction (Namkung et al., 2015; Zhang et al., 2015). As stated earlier, Trp is a precursor for the biosynthesis of 5-hydroxytryptamine (5HT, serotonin). Serotonin is a neurotransmitter and biochemical regulator, which contributes to satiety and hunger balance. Gustatory information during the act of eating is transmitted to the nucleus accumbent, which is typically considered the reward center. This leads to the release or the up-regulation of serotonin and opiates, which are called the "reward mediators". Likewise, appetite-controlling neurons are connected to specialized brain regions (Halford and Blundell, 2000).

Overeating and obesity are the results of diet including palatable food, where the time spent eating will be prolonged due to suppressed satiety (Brandacher et al., 2007). In this context, serotonin as neurotransmitter may be involved in the control of food intake, which is a satiety signal (Halford and Blundell, 2000). Moreover, this process is responsible for the inhibition of the expression of neuropeptides Y, which occur in the hypothalamus, through depressing hunger and control of body adiposity (Wurtman and Wurtman, 1995; Manousopoulou et al., 2016). Also, it has been found that serotonin specifically regulates fat and/or carbohydrate intake (Blundell and Lawton, 1995; Bray, 2001).

3. Anorexia nervosa and bulimia nervosa

Eating disorders (EDs) are widespread and serious diseases throughout the world, with a chronic course and potentially fatal outcome (Winkler et al., 2016). Genetic and environmental factors contribute to the development of many complex eating disorders (Haleem, 2012). The most common eating disorders may include anorexia nervosa (AN) and bulimia nervosa (BN). Both diseases are disorders of considered to arise from unknown etiology. They usually begin during adolescence in women, but may also be seen in men (Becker et al., 2003; Kaye et al. 2005, 2008; Haleem 2012).

A study conducted by Haleem (2012) suggested that females are more vulnerable to food restriction, which may start with a chronic deficiency in Trp levels and bioavailability. Monoaminergic neurotransmitters such as serotonin (5-HT), noradrenaline (NA) and dopamine (DA) contribute to the regulation feeding behavior, while the accessibility of precursor amino acids in the blood powerfully influences the synthesis of those monoamines in the brain (Ehrlich et al., 2009).

The most common symptoms of eating disorders are restricted eating, body image distortions, and denial of emaciation, binge-purge behaviors, and resistance to treatment. They are also characterized by aberrant patterns of weight regulation and feeding behavior, but also by different perceptions towards shape and body weight, dysphoric mood exhibit behaviors, such as perfectionism and obsessive–compulsiveness. AN and BN are relapsing and often are chronic disorders, whereas AN has the highest death rate compared to other psychiatric disorders.

Patients with AN accompanied an obsession with body weight and inexplicable fear of weight gain, even in the face of the increasing destruction of the body, characteristically exhibit motor

restlessness and excessive exercise (Kaye et al., 2001). The main role in behavioral changes observed in a patient with anorexia nervosa presents anomalies occurring in the serotoninergic pathway. In AN an individual's serotonin level is involved in almost all the behavioral changes. Patients with AN show higher frequency of compulsive exercising relative to those with BN patients (Haleem, 2012). After a period of food restriction, the sufferer usually emerges with BN. They may or may not have been linked with weight loss. After surfeit followed by self-induced vomiting or different way compensation of surfeit, people suffering from BN also have a fear of weight gain and distorted view of their body shape. Individuals with BN are impulsive, and often sensation seeking, whereas individuals with AN tend toward emotional expressiveness and constriction of affect, and may exhibit great constraint.

The above-described characteristics of anorexia nervosa and bulimia nervosa often begin in childhood, are premorbid and often persist even after recovery. This would suggest that such behavior caused by underfeeding is not secondary. Dysregulation of impulse control and appetite or mood in AN and BN contributes modified brain serotonin function. The occurrence of AN precedes the disturbance of neuronal serotonin modulation, which contributes to premorbid symptoms of inhibition, anxiety, and obsessionality. In patients with BN, it has been observed that dietary depletion of Trp is associated with Trp-associated mood irritability and increased food intake, which is caused by dysfunction of serotonergic tone (Kaye et al., 2005, 2008). Because Trp is the precursor to serotonin, Trp deficit could significantly alter serotoninergic neurotransmission. In the refeeding, the Trp/LNAA ratio increases, as it associated with a decrease in depressive symptoms. This fact provides an argument for a possible impact of the AN mood symptoms with the serotoninergic pathway through a normalization of the biological

markers. The increase in the Trp/LNAA ratio is possible by the intake of related essential amino acids. The transport of Trp is predictive through the blood-brain barrier towards the cerebrospinal fluid (CSF) in the evaluation of the Trp/LNAA ratio. Then, Trp can be used for the synthesis of cerebral serotonin. In these particular ways, the serotoninergic transfer, which leads to a decrease in depressive symptoms, is restored (Gauthier et al., 2014). For all patients with EDs, common features include dysfunctional cognizance relating to shape and weight and result in restrained eating behaviors.

In the literature, there is lots of evidence of anxiety, appetite dysregulation, extremes of impulse control and obsessional behaviors, caused by disturbances 5-HT in those suffering from EDs. Enhancement of the brain serotonin release, which can affect appetite regulation, can determine meal consumption, depending on the amount of protein and carbohydrate in the meal. Carbohydrate consumption causes depletion of the large neutral amino acids valine, leucine, isoleucine, phenylalanine and tyrosine. This LNAA competes with Trp for uptake into the brain. Such elevates the plasma Trp/LNAA ratio, thereby the amount of Trp in the brain, causing rapid synthesis and release of 5-HT. In contrast, a diet rich in proteins can block those effects, resulting in the large amounts of LNAA in the blood (Fernstrom et al., 1979; Kaye et al., 2005, 2008). The results of many studies indicate a decrease in plasma of the Trp/LNAA ratio and Trp levels in patients with acute underweight (Schreiber et al., 1991; Askenazy et al., 1998; Ehrlich et al., 2009; Comai et al., 2010; Gauthier et al., 2014).

A broader viewpoint is shown by Gauthier et al. (2014), where they show links between serotonin biomarkers, nutritional status and psychological states in anorexia nervosa conjointly. For the first time, they were able to highlight the role of the low level of Trp in plasma, blood

serotonin, and LNAA and Trp/LNAA ratio with malnutrition (Gauthier et al., 2014). They also found a positive correlation between anxiety, depression score, and total blood serotonin levels in a group of AN individuals classified as an impulsive. These results are consistent with the results obtained by other teams. Acute Trp depletion in AN patients was found to lead to an increase in anxiety. Through the restrictive dietary behaviors, individuals may decrease cerebral serotonin synthesis. Additionally, reduced 5-HT concentrations in hypothalamic causes hyperactivity, which intensifies behaviors leading to weight loss. The emergence of BN symptoms and amplified impulsivity appear to be related to low serotonin levels. This may explain the frequent overlap between the restrictive forms of AN and the bulimic state, and behaviors are alternating between these eating disorders (Gauthier et al., 2014).

4. Autism spectrum disorder

Autism spectrum disorder (ASD) is a developmental, multifactorial disorder, characterized by symptoms that evolve with age adversely affecting the development of the child (Bara et al., 2001). The incidence of ASD has grown worldwide by 600% since the 1970s. In the US, currently at least one of 68 children has ASD (Zablotsky et al., 2015; Christensen et al., 2016). Patients with ASD demonstrate the problem with interacting and exhibit little interest in others and lack of social awareness (Kałużna-Czaplińska and Błaszczyk, 2012). Etiology and pathogenesis of ASD are not still fully known. However, evidence points to nutritional deficiencies or overloads, complex genetic interactions, maternal age and health state, exposure to chemicals or viruses, heavy metal toxicity, immunological overload from early vaccinations, certain food additives, and dysfunctional immune systems or allergies. Deficiencies in the levels of amino acids occur for many children with developmental disorders.

In recent years, observations relative to metabolic biomarkers have shed light on the influence of amino acids on various developmental disorders. In some cases, the neurological function could be specified just by studies of amino acids. Some researchers have suggested that a pivotal role in ASD might be found with Trp metabolism. A metabolite of Trp is the neurotransmitter serotonin (5-HT), which is, among other things, responsible for regulating humor and behavior, and also facilitating calmness, feeling of well-being, relaxation, personal security, concentration, and self-confidence. Hence, reduced serotonin levels have been demonstrated to influence many developmental disorders. For this reason, it is reasonable to posit a connection between escalation of autistic symptoms and abnormal levels of serotonin (Adams and Holloway, 2004). Likewise, a dysfunctional serotonergic system could be involved with ASD. As stated above, Trp is converted into serotonin in the brain, where it competes for transport with nine other large, neutral amino acids (LNAA) (Beretich, 2009).

Many children with ASD exhibit a deficiency in Trp due to significant food selectivity and self-imposed diet restriction. This often leads to reduced levels of serotonin and a worsening of autistic behaviors. The literature mentions that urinary excretion of Trp might be caused by a low concentration of dietary proteins. In 1986, research suggested a link between some problems in children with ASD and abnormal Trp metabolism. The results indicated that free plasma Trp levels were evaluated in ASD children compared to healthy children and adult controls (Hoshino et al., 1986). Therefore, biochemical abnormalities were associated with a significantly lower level of Trp in urine.

More recently, researchers examined 54 children aged 4--10 years, 33 ASD children (4 female and 29 males) and 21 normal children as healthy controls (8 females and 13 males)—the gender

ratios in the subjects under study, incidentally, were about the same as found in other studies. The ASD children were divided into a group of 10 children with ASD on the restricted diet low casein and gluten, and 23 ASD children without restricted diet. The highest values of Trp in urine were observed in control group. Significantly lower concentration levels of Trp were reported in the samples from 23 ASD children that were on the restricted diet. Low levels of Trp might also cause intensification of the symptoms of ASD, such as increased irritability and mild depression (Kałużna-Czaplińska et al., 2010). McDougle et al. (1993) have received similar results about low diet in Trp. The researchers also suggested that by depleting Trp in an adult with ASD they might induce significant changes in behavior, which were not seen in that control group such as increasing whirling, banging, hitting self, rocking, and toe walking (McDougle et al., 1996).

Other scientists focused on the relationship between developmental disorders and metabolic disturbances. Researchers examined 55 children ages 5--16 years with ASD and 44 healthy controls of similar age, gender, and geographical distribution. The study was aimed at comparing the metabolic and nutritional status of ASD children with that of control children and investigated autism severity to the Trp-related biomarkers. Results showed significantly decreased Trp in the children with ASD. This might be due to reduced protein intake, and dysfunction in synthesizing protein into amino acids in the digestive tract. Decreased Trp could further impair serotonin synthesis. A deficiency of Trp and thus serotonin lead to a significant worsening in behavior in ASD participants (Adams et al., 2011).

Similar results were also found in other studies. For example, Naushad et al. (2013) examined 138 autistic children, 120 males and 18 females, and 138 non-autistic controls, 120 males and 18

females. Children were matched for age, gender, ethnicity and geographical area. Researchers observed markedly lower levels of Trp in the ASD children (Trp levels decreased by an average of 48%), compared to healthy controls (Naushad et al., 2013).

5. Parkinson and Alzheimer diseases

The pathogenesis of neurodegenerative disorders such as Parkinson's (PD) and Alzheimer's diseases (AD) are not entirely known. However, it is believed that in this pathogenic process are involved immunologic mechanisms. In the development and progression of PD and AD, a cause has been ascribed to stimulate immunocompetent cells and a significant number of (proinflammatory) cytokines (Widner et al., 2002). Parkinson's disease categorically belongs to chronic, progressive, and irreversible neurodegenerative diseases, which are caused mainly by the progressive degeneration of the dopaminergic pathway. The second most common neurodegenerative disease among older adults is PD. So far, the disease has long been considered a disease of old age (over 60 years of age), but it also occurs increasingly in younger people. When the damage of dopaminergic neurons reaches 50--60%, and the striatum does not reach adequate dopaminergic input, there arise characteristic motor symptoms and behaviors (Andersen et al., 2017).

Symptoms and signs of PD are resting tremor, curved posture, bradykinesia, rigidity, depression, and postural instability, shuffling gait. For severe disability progressively lead to long–term complications of dopaminergic treatment, which focuses on minimizing the symptoms like motor blocks and dyskinesia. The close relationship might observe between neurodegenerative diseases and nutritional status (Barichella et al., 2009). PD is very difficult, if not impossible, to diagnose before motor symptoms have begun developing. Other symptoms associated with early stage

disease are very unspecific including obstipation, olfactory deficiency, depression, and sleep disorders (Andersen et al., 2017).

Increased risk of PD can relate to many factors, such as consumption of (processed) dairy products, past traumatic brain injury, heavy metal toxicity, certain food additives, polypharmacy, certain parasites, and exposure to pesticides and even history of melanoma (although this latter factor appears strictly correlational). In contrast, the factors that reduce the risk of occurring PD are associated with caffeine consumption, smoking, physical activity, and higher serum urate concentrations of NSAIDs. Caffeine, nicotine, and urate may be neuroprotective and give benefits in patients with early PD. Whether this mild evidence is offset by the other more serious detriments implicated by caffeine, nicotine, and NSAIDs is another matter. Researchers are looking for possible ways to identify this disease in its early stages and possibly using (healthy) neuroprotective interventions before the presentation of motor symptoms (Ascherio and Schwarzschild, 2016).

Tryptophan is the precursor not only of serotonin, but also is degraded to the kynurenic acid, 3-hydroxykynurenine, and quinolinic acid. Kynurenine pathway that regulates the synthesis of these neuroactive metabolites. The human immune system controls the kynurenine pathway. Hyperfunction or hypofunction of neuroactive metabolites is caused by dysregulation of the kynurenine pathway, which relates closely to neurological and neurodegenerative disorders. The concentration of 3-hydroxykynurenine (3-HK) is increased in the basal ganglia of PD patients, whereas kynurenic acid (KYNA) and kynurenine levels are slightly reduced (Ogawa et al., 1992; Schwarcz et al., 2012). The strongest quinolinic acid (QUIN) is found in glial cells. This fact suggests that QUIN might participate in the pathogenic process in Alzheimer's disease

(Guillemin et al., 2005; Schwarcz et al., 2012). Interferon γ (INF- γ) product large amounts of neopterin, wherein IFN-γ induces indoleamine 2,3-dioxygenase (IDO), which causes degradation L-tryptophan to kynurenine.

In the literature, there are reports on high concentrations of neopterin, Trp, and kynurenine found in serum and CSF samples. Widner et al. (2002) examined 22 patients with PD (15 females and seven males) and 11 age-matched controls group, without obvious neuropsychiatric symptoms (6 females and five males). From eight patients with PD were collected cerebrospinal fluid specimens. The results showed significantly higher concentrations of neopterin and kynurenine/Trp ratio (kyn/trp ratio) and lower Trp concentrations in serum samples of PD patients compared to healthy controls. Similar relationships were found in CSF from eight PD patients. Comparing the two body fluids, serum neopterin concentrations were higher than in CSF. It can be assumed that reduced dietary intake of Trp could significantly contribute to Trp depletion in PD patients (Widner et al., 2002). Similar results were obtained by Ogawa et al. (1992) who observed in PD patients increased the level of 3-hydroxykynurenine (3-HA), while the level of KYNA decreased.

The search for new biomarkers is always scientific interest. Lewitt et al. (2013) employed targeted metabolomics, using CSF from PD patients and controls. They observed changes in the ratio of 3-hydroxykynurenine (3-HK)/kynurenic acid (KYNA). This variation in the ratio 3-HK/KYNA is significant because 3-HK is a precursor of the quinolinic acid and by general hydroxyl radicals might cause oxidative damage. Whereas KYNA has neuroprotective potential. Promote neurodegeneration in the brain might cause an increased ratio of 3-HK/KYNA (Lewitt et al., 2013). In another study, Mollenhauer and Zhang (2013) tried to unveil the candidate

metabolic pathway related to PD. They examined 35 patients with PD without dementia, and as a control group, 15 healthy age-matched participants without PD. The results showed that metabolomic profiles of patients with PD were substantially different from control groups. PD profiles had significantly lower levels of Trp. Decreased serum Trp levels appear to be significantly related to psychiatric problems in patients with PD (Mollenhauer and Zhang, 2013).

Alzheimer's disease was first described more than a century ago. This disease affects approximately 35.6 million people worldwide in 2010 and by the year 2050 estimated 115 million people (Van Wijngaarden et al., 2017). One of the major causes of dementia is AD. So far, the pathogenesis of this disease is not completely understood. It is, however, well known that the kynurenine pathway is the principal route for the metabolism of the Trp. Among other metabolic pathways, Trp is the kynurenine pathway involved in AD pathogenesis (Kincses et al., 2010). Hence, changes in AD behaviors have been observed in the kynurenine pathway. These changes are based on a reduction in the serum concentration of KYNA and Trp and in increased concentrations of 3- hydroxykynurenine (3-HA) and kynurenine (O'Farrell and Harkin, 2017).

The mechanism of AD is similar to other neurodegenerative diseases such PD. Mechanisms of AD are associated with the kynurenine pathway (KP). Many proinflammatory cytokines activate kynurenine pathway, and then they create metabolites associated with the pathogenesis of AD. For limiting kynurenine pathway responsible is indoleamine-2-3 dioxygenase (IDO). The expression of IDO is markedly increased with the proliferation of proinflammatory cytokines INF-γ. Overexpression of IDO is induced by INF-γ in the presence of amyloid plaques, which leads to dysregulation of KP. In dysregulation of KP is also involved interleukin-18 (IL-18), which induces strong inflammatory reactions. IL-18 appears to be responsible for the production

of neurotoxic QUIN, wherein is promoted neurodegeneration. Furthermore, QUIN may cause an increased level of lipid peroxidation in oxidative stress and may provoke neuronal death by cytotoxicity. In AD patients, unchanged levels of QUIN in cerebral and CSF have been observed, whereas the level of KYNA was increased in the striatum, but in CSF and plasma, the level of KYNA was decreased. At this time, there is still no clear explanation concerning to how decrease KYNA levels that contribute to Alzheimer's disease (Tan et al., 2012).

Kincses et al. (2010) presented evidence of the participation of the kynurenine pathway in the pathogenesis of AD. They measured the kynurenine, Trp and KYN/Trp ratio in the plasma. Examined were ten patients with AD (six females and four males) and 15 healthy controls (11 females and four males). The results showed that Trp concentration was significantly lower in AD patients than controls, while KYN showed no significant differences between AD patients compared to controls, and the KYN/Trp ratio was considerably higher in patients with AD (Kincses et al., 2010).

In the pathogenesis of AD, inflammation and immune activation are factors related to increased blood concentration of certain biomarkers, such as the kynurenine to Trp ratio (KYN/Trp) and neopterin. Wissmann et al. (2013) examined 43 AD patients (26 females and 17 males, range aged 57--99 years), they measured neopterin, Trp, and kynurenine concentration. They observed lower Trp levels, higher kynurenine levels, and a higher KYN/Trp ratio, which is correlated with the higher concentration of neopterin. (Wissmann et al., 2013). Similar results were obtained by Widner et al. (1999), which examined 24 patients with AD and observed lower Trp levels, higher kynurenine levels, and KYN/Trp ratio.

Other scientists examined the concentrations of the compound in CSF of patients with AD. They explored correlations between KYNA levels, well-established AD, cognitive decline and proinflammatory markers. Then they measured KYNA levels in 19 AD patients, aged 72--79 years, and 20 healthy controls, age matched. The results showed that AD patients have significantly KYNA levels versus the healthy controls. Additionally, they observed that female AD patients had significantly higher KYNA levels compared to male AD patients, wherein this result was not observed in the healthy control group (Wennström et al., 2014).

6. Tryptophan and sleep disorders

Sleep disorders are a serious problem in industrialized societies and concerns not only adults but also children and young people. It is estimated that sleep disorders affect at least 20--40% of adults, and half of them consider it to be important. Likewise, various types of sleep difficulties concern 25--62% of the population of children, depending on their stage of development (Blader et al., 1997; Kaczor and Skalski, 2016).

In recent years, experts were interested in the relationship between sleep and diet. The basis for the discussion of the problem is the enzyme pathway of melatonin synthesis, which precursor for melatonin is serotonin. This, in turn, is synthesized by enzymatic transformation of Trp (Kaczor and Skalski, 2016).

Hormones produced in the brain, such as serotonin and melatonin, control sleep and circadian rhythms in humans. Melatonin is an active biological compound that is responsible for regulating diurnal rhythms and influences the immune and reproductive system, and gastrointestinal motility and other digestive processes. The pineal gland secretes melatonin during periods of darkness. Its task is to regulate circadian rhythms and sleep patterns (Richard et al., 2009;

Szczepanik, 2007). Tryptophan is often used for the treatment of sleep disorders. In the diet Trp produces therapeutic effects through melatonin. A crucial feature of Trp treatment is that it does not directly reduce cognitive ability (Richard et al., 2009).

One hypothesis is that sunlight accelerates serotonin synthesis. Studies in Japan suggest that combined intervention of a breakfast rich in Trp, regular morning sun exposure, and evening lighting combine to improve higher melatonin secretion at night. Associated with this was found improved sleep quality and reduced time required to fall asleep (Nakade et al., 2012; Wada et al., 2013).

Infant sleep problems constitute a serious disorder and might affect brain development (and be implicated in other more serious health problems, as well). In the literature, there is a report about the impact of diet on improving the conditions of sleep. Cubero et al. (2009) examined 30 children with sleep problems, aged 8--16 months old. In the evening meal, they administrated to infants were cereals with varying content of Trp over a five-week period. Feeding of enriched cereals led to the maintenance of calmer children and restored sleep. They concluded that regulation of circadian cycle can be influenced by diet (Cubero et al., 2009).

One of many sleep disorders is night terrors. Sharp waking from sleep characterizes night terrors, accompanied by persistent terror and fear or increased heart rate, sweating, and screaming. Promising results have been demonstrated that Trp supplementation for night terrors. Bruni et al. (2004) examined the influence L-5-hydroxytryptophan on sleep terrors. They studied 45 children (34 males and 11 females, aged 3.2-10.6 years) safer from sleep terrors. The studied group was supplementation by L-5-hydroxytryptophan. Within a month, they observed a reduction of more than half night terror episodes in over 93% of children. These results confirm that arousal level

might be positively influenced by treatment with L-5-hydroxytryptophan, resulting in reduced sleep terror behaviors in children (Bruni et al., 2004).

7. Conclusion

The interest in Trp is growing throughout research and health community worldwide (**Figure 2**). The role of Trp in the relationship serotonin-Trp uptake with diet is particularly intriguing and deserves much more insightful data to achieve a forthright and clearer conclusion. Certainly, research in the nutritional fields must be further investigated and implemented, to elucidate the role of supplemented Trp in foods and meals that improve human health and prevent many serotonin-related pathologies. We believe that an optimized and personalized diet can help to minimize the symptoms of illness, which will result in improved health.

References

Adams, J. B., and Holloway, C. (2004). Pilot study of a moderate dose multivitamin/mineral supplement for children with autistic spectrum disorder. *J Altern Complement Med*. **10**: 1033--1039.

Adams, J. B., Audhya, T., McDonough-Means, S., Rubin, R. A., Quig, D., Geis, E., Gehn, E., Loresto, M., Mitchell, J., Atwood, S., Barnhouse, S., and Lee, W. (2011). Nutritional and metabolic status of children with autism vs. neurotypical children, and the association with autism severity. *Nutr Metab (Lond)*. **8**: 34.

Andersen, A. D., Binzer, M., Stenager, E., and Gramsbergen, J. B. (2017). Cerebrospinal fluid biomarkers for Parkinson's disease – a systematic review. *Acta Neurol Scand.* **135**: 34--56.

André, C., Dinel, A. L., Ferreira, G., Layé, S., and Castanon, N. (2014). Diet-induced obesity progressively alters cognition, anxiety-like behavior and lipopolysaccharide-induced depressive-like behavior: focus on brain indoleamine 2,3-dioxygenase activation. *Brain Behav Immun.* **41**: 10--21.

Ascherio, A., and Schwarzschild, M. A. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol.* **15**: 1257--1272.

Askenazy, F., Candito, M., Caci, H., Myquel, M., Chambon, P., Darcourt, G., and Puech, A. J. (1998). Whole blood serotonin content, tryptophan concentrations, and impulsivity in anorexia nervosa. *Biol Psychiatry*. **43**: 188--195.

Atkinson, W., Lockhart, S., Whorwell, P. J., Keevil, B., and Houghton, L. A. (2006). Altered 5-hydroxytryptamine signaling in patients with constipation- and diarrhea-predominant irritable bowel syndrome. *Gastroenterology*. **130**: 34--43.

Bara, B. G., Bucciarelli, M., and Colle, L. (2001). Communicative abilities in autism: evidence for attentional deficits. *Brain Lang*. **77**: 216--240.

Barichella, M., Cereda, E., and Pezzoli, G. (2009). Major nutritional issues in the management of Parkinson's disease. *Mov Disord.* **24**: 1881--1892.

Becker, A. E., Burwell, R. A., Navara, K., and Gilman, S. E. (2003). Binge eating and binge eating disorder in a small-scale, indigenous society: the view from Fiji. *Int J Eat Disord*. **34**: 423--431.

Beretich, G. R. (2009). Reversal of autistic symptoms by removal of low-relative tryptophan foods: case report. *Med Hypotheses.* **73**: 856--857.

Blader, J. C., Koplewicz, H. S., Abikoff, H., and Foley, C. (1997). Sleep problems of elementary school children. A community survey. *Arch Pediatr Adolesc Med*. **151**: 473--480.

Blundell, J. E., and Lawton, C. L. (1995). Serotonin and Dietary Fat Intake: Effects of Dexfenfluramine. *Metabolism*. **44**: 33--37.

Brandacher, G., Hoeller, E., Fuchs, D., and Weiss, H. G. (2007). Chronic immune activation underlies morbid obesity: is IDO a key player? *Curr Drug Metab*. **8**: 289--295.

Bray, G. A. (2001). Drug Treatment of Obesity. *Rev Endocr Metab Disord*. **2**: 403--418.

Bruni, O., Ferri, R., Miano, S., and Verrillo, E. (2004). L -5-Hydroxytryptophan treatment of sleep terrors in children. *Eur J Pediatr*. **163**: 402--407.

Caballero, B., Finer N., and Wurtman R. J. (1988). Plasma amino acids and insulin levels in obesity: response to carbohydrate intake and tryptophan supplements. *Metabolism*. **37**: 672--676.

Catanzaro, R., Occhipinti, S., Calabrese, F., Anzalone, M. G., Milazzo, M., Italia A., and Marotta, F. (2014). Irritable bowel syndrome: new findings in pathophysiological and therapeutic field. *Minerva Gastroenterol Dietol*. **60**: 151--63.

Catrysse, L., and Van Loo, G. (2017). Inflammation and the Metabolic Syndrome: The Tissue-Specific Functions of NF-κB. *Trends Cell Biol.* **8924**: 30024--30027.

Christensen, D. L., Baio, J., Braun, K. V., Bilder, D., Charles, J., Constantino, J. N., Daniels, J., Durkin, M. S., Fitzgerald, R. T., Kurzius-Spencer, M., Lee L. C., Pettygrove, S., Robinson, C., Schulz, E., Wells, C., Wingate, M. S., Zahorodny, W., and Yeargin-Allsopp, M. (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years – Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2012. *MMWR Surveillance Summaries*, **65**: 1–23.

Comai, S., Bertazzo, A., Carretti, N., Podfigurna-Stopa, A., Luisi, S., and Costa, C. V. (2010). Serum levels of tryptophan, 5-hydroxytryptophan and serotonin in patients affected with different forms of amenorrhea. *Int J Tryptophan Res.* **3**: 69--75.

Comai, S., Bertazzo, A., Vachon, J., Daigle, M., Toupin, J., Côté, G., Turecki, G., and Gobbi, G. (2016). Tryptophan via serotonin/kynurenine pathways abnormalities in a large cohort of aggressive inmates: markers for aggression. *Prog Neuropsychopharmacol Biol Psychiatry*. **70**: 8--16.

Cubero, J., Chanclón, B., Sánchez, S., Rivero, M., Rodríguez, A. B., and Barriga, C. (2009). Improving the quality of infant sleep through the inclusion at supper of cereals enriched with tryptophan, adenosine-5'-phosphate, and uridine-5'-phosphate. *Nutr Neurosci*. **12**: 272--280.

Davies, S. K., Ang, J. E., Revell, V. J., Skene, D. J., Manna, A., Robertsona, F. P., Cuia, N., Middletona, B., Ackermannc, K., Kayserc, M., Thumsera, A. E., Raynaudb, F. I., and Skenea,

D. J. (2014). Effect of sleep deprivation on the human metabolome. *Proc Natl Acad Sci U S A.* **111**(29).

de Figueiredo, L. F., Gossmann, T. I., Ziegler, M., and Schuster, S. (2011). Pathway analysis of NAD+ metabolism. *Biochem J.* **439**: 341--348.

Drossman, D. A., Camilleri, M., Mayer, E. A., and Whitehead, W. E. (2002). AGA technical review on irritable bowel syndrome. *Gastroenterology.* **123**: 2108--2131.

Dunlop, S. P., Coleman, N. S., Blackshaw, E., Perkins, A. C., Singh, G., Marsden, C. A., and Spiller, R. C. (2005). Abnormalities of 5-hydroxytryptamine metabolism in irritable bowel syndrome. *Clin Gastroenterol Hepatol*. **3**: 349--357.

Ehrlich, S., Franke, L., Schneider, N., Salbach-Andrae, H., Schott, R., Craciun, Pfeiffer, E., Uebelhack, R., and Lehmkuhl, U. (2009). Aromatic amino acids in weight-recovered females with anorexia nervosa. *Int J Eat Disord*. **42**: 166--172.

Fernstrom, J. D., Wurtman, R. J., Hammarstrom-Wiklund, B., Rand, W. M., Munro, H. N., and Davidson, C. S. (1979). Diurnal variations in plasma concentrations of tryptophan, tryosine, and other neutral amino acids: effect of dietary protein intake. *Am J Clin Nutr*. **32**: 1912--1922.

Fitzgerald, P., Cassidy Eugene, M., Clarke, G., Scully, P., Barry, S., Quigley Eamonn, M. M., Shanahan, F., Cryan, J., and Dinan, T. G. (2008). Tryptophan catabolism in females with irritable bowel syndrome: relationship to interferon-gamma, severity of symptoms and psychiatric co-morbidity. *Neurogastroenterol Motil*. **20**: 1291--1297.

Gauthier, C., Hassler, C., Mattar, L., Launay, J. M., Callebert, J., Steiger, H., Melchior, J. C., Falissard, B., Berthoz, S., Mourier-Soleillant, V., Lang, F., Delorme, M., Pommereau, X.,

Gerardin, P., Bioulac, S., Bouvard, M., EVHAN Group, and Godart N. (2014). Symptoms of depression and anxiety in anorexia nervosa: links with plasma tryptophan and serotonin metabolism. *Psychoneuroendocrinology*, **39**: 170--178.

Grundmann, O., Yoon, S. L., and Moshiree, B. (2010). Current developments for the diagnosis and treatment of irritable bowel syndrome. *Curr Pharm Des*. **16**: 3638--3645.

Guillemin, G. J., Brew, B. J., Noonan, C. E., Takikawa, O., and Cullen, K. M. (2005). Indoleamine 2,3 dioxygenase and quinolinic acid immunoreactivity in Alzheimer's disease hippocampus. *Neuropathol Appl Neurobiol.* **31**: 395--404.

Haleem, D. J. (2012). Serotonin neurotransmission in anorexia nervosa. *Behav Pharmacol.* **23**: 478--495.

Halford, J. C., and Blundell, J. E., (2000). Separate systems for serotonin and leptin in appetite control. *Ann Med.* **32**: 222--232.

Heitkemper, M. M., Han, C. J., Jarrett, M. E., Gu, H., Djukovic, D., Shulman, R. J., Raftery, D., Henderson, W. A., and Cain, K. C. (2016). Serum Tryptophan Metabolite Levels During Sleep in Patients With and Without Irritable Bowel Syndrome (IBS). *Biol Res Nurs*. **18**: 193--198.

Hoshino, Y., Yamamoto, T., Kaneko, M., and Kumashiro, H. (1986). Plasma free tryptophan concentration in autistic children. *Brain Dev*. **8**: 424--427.

Houghton, L. A., Atkinson, W., Whitaker, R. P., Whorwell, P. J., and Rimmer, M. J. (2003). Increased platelet depleted plasma 5-hydroxytryptamine concentration following meal ingestion in symptomatic female subjects with diarrhoea predominant irritable bowel syndrome. *Gut*. **52**: 663--670.

Hulsken, S., Märtin, A., Mohajeri, M. H., and Homberg, J. R. (2013). Food-derived serotonergic modulators: effects on mood and cognition. *Nutr Res Rev*. **26**: 223--234.

Hundal, R. S., Krssak, M., Dufour, S., Laurent, D., Lebon, V., Chandramouli, V., Inzucchi, S. E., Schumann, W. C., Petersen, K. F., Landau, B. R., and Shulman, G. I. (2000). Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes*. **49**: 2063--2069.

Kaczor, M., and Skalski, M. (2016). Treatment of behavioral sleep problems in children and adolescents – literature review. *Psychiatr Pol.* **50**: 517--584.

Kałużna-Czaplińska, J., and Błaszczyk, S. (2012). The level of arabinitol in autistic children after probiotic therapy. *Nutrition*, **28**: 124--126.

Kałużna-Czaplińska, J., Michalska, M., and Rynkowski, J. (2010). Determination of tryptophan in urine of autistic and healthy children by gas chromatography/mass spectrometry. *Med Sci Monit*. **16**: 488--492.

Kałużna-Czaplińska, J., Żurawicz, E., Struck, W., and Markuszewski, M. (2014). Identification of organic acids as potential biomarkers in the urine of autistic children using gas chromatography/mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci*. **966**: 70--76.

Karu, N., McKercher, C., Nichols, D. S., Davies, N., Shellie, R. A., Hilder, E. F., and Jose, M. D. (2016). Tryptophan metabolism, its relation to inflammation and stress markers and association with psychological and cognitive functioning: Tasmanian Chronic Kidney Disease pilot study. *BMC Nephrol*. **17**:171.

Kaye, W. (2008). Neurobiology of anorexia and bulimia nervosa. *Physiol Behav*. **94**: 121--135.

Kaye, W. H., Frank, G. K., Bailer, U. F., Henry, S. E., Meltzer, C. C., Price, J. C., Mathis, C. A., and Wagner, A. (2005). Serotonin alterations in anorexia and bulimia nervosa: new insights from imaging studies. *Physiol Behav.* **85**: 73--81.

Kaye, W. H., Gendall, K. A., Fernstrom, M. H., Fernstrom, J. D., McConaha, C. W., and Weltzin, T. E. (2000). Effects of acute tryptophan depletion on mood in bulimia nervosa. *Biol Psychiatry*. **47**: 151--157.

Kaye, W. H., Gwirtsman, H.E., George, D. T., Jimerson, D. C., and Ebert, M. H. (1988). CSF 5-HIAA concentrations in anorexia nervosa: reduced values in underweight subjects normalize after weight gain. *Biol Psychiatry*. **23**: 102--105.

Kaye, W., Gendall, K., and Strober, M. (2001). Nutrition, serotonin and behavior in anorexia and bulimia nervosa. *Nestle Nutr Workshop Ser Clin Perform Programme*. **5**: 153--168.

Keszthelyi, D., Troost, F. J., Jonkers, D. M., Van Donkelaar, E. L., Dekker, J., Buurman, W. A., and Masclee, A. A. (2012). Does acute tryptophan depletion affect peripheral serotonin metabolism in the intestine? *Am J Clin Nutr.* **95**: 603--608.

Kilkens, T. O., Honig, A., van Nieuwenhoven, M. A., Riedel, W. J., and Brummer, R. J. (2004). Acute tryptophan depletion affects brain-gut responses in irritable bowel syndrome patients and controls. *Gut*. **53**: 1794--1800.

Kincses, Z. T., Toldi, J., and Vécsei, L. (2010). Kynurenines, neurodegeneration and Alzheimer's disease. *J Cell Mol Med*. **14**: 2045--2054.

Klempel, M. C., and Varady, K. A. (2011). Reliability of leptin, but not adiponectin, as a biomarker for diet-induced weight loss in humans. *Nutr Rev*. **69**: 145--54.

Lewitt, P. A., Li, J., Lu, M., Beach, T. G., Adler, C. H., Guo, L., and Arizona Parkinson's Disease Consortium. (2013). 3-hydroxykynurenine and other Parkinson's disease biomarkers discovered by metabolomic analysis. *Mov Disord*. **28**: 1653--1660.

Liu, W., Mi, S., Ruan, Z., Li, J., Shu, X., Yao, K., Jiang, M., and Deng, Z. (2017). Dietary Tryptophan Enhanced the Expression of Tight Junction Protein ZO-1 in Intestine. *J Food Sci*. **82**: 562--567.

Longstreth, G. F., Thompson, W. G., Chey, W. D., Houghton, L. A., Mearin, F., and Spiller, R. C. (2006). Functional bowel disorders. *Gastroenterology*. **130**: 1480--1491.

Lönnqvist, F., Arner, P., Nordfors, L., and Schalling, M. (1995). Overexpression of the obese (ob) gene in adipose tissue of human obese subjects. *Nat Med*. **1**: 950--953.

Luan, H., Liu, L. F., Tang, Z., Zhang, M., Chua, K. K., Song, J. X., Mok, V. C., Li, M., and Cai, Z. (20015). Comprehensive urinary metabolomic profiling and identification of potential noninvasive marker for idiopathic Parkinson's disease. *Sci Rep.* **5**:13888.

Madara, J.L., and Carlson, S. (1991). Supraphysiologic L-tryptophan elicits cytoskeletal and macromolecular permeability alterations in hamster small intestinal epithelium in vitro. *J Clin Invest*. **87**: 454--62.

Mangge, H., Summers, K. L., Meinitzer, A., Zelzer, S., Almer, G., Prassl, R., Schnedl, W. J., Reininghaus, E., Paulmichl, K., Weghuber, D., and Fuchs, D. (2014). Obesity-related dysregulation of the tryptophan-kynurenine metabolism: role of age and parameters of the metabolic syndrome. *Obesity (Silver Spring)*. **22**: 195--201.

Manousopoulou, A., Koutmani, Y., Karaliota, S., Woelk, C. H., Manolakos, E. S., Karalis, K., and Garbis, S. D. (2016). Hypothalamus proteomics from mouse models with obesity and anorexia reveals therapeutic targets of appetite regulation. *Nutr Diabetes*. **6**:e204.

McDougle, C. J., Naylor, S. T., Cohen, D. J., Aghajanian, G. K., Heninger, G. R., and Price, L. H. (1996). Effects of tryptophan depletion in drug-free adults with autistic disorder. *Arch Gen Psychiatry*. **53**: 993--1000.

McDougle, C. J., Naylor, S. T., Goodman, W. K., Volkmar, F. R., Cohen, D. J., and Price, L. H. (1993). Acute tryptophan depletion in autistic disorder: a controlled case study. *Biol Psychiatry*. **33**: 547--550.

Ming, X., Stein, T. P., Barnes, V., Rhodes, N., and Guo, L. (2012). Metabolic perturbance in autism spectrum disorders: a metabolomics study. *J Proteome Res*. **11**: 5856--5862.

Mollenhauer, B., and Zhang, J. (2013). Biochemical Pre-motor Biomarkers for Parkinson Disease. *Mov Disord.* **27**: 644--50.

Moskwa, A., Wiśniewska – Jarosińska, M., Stec-Michalska, K., Szadkowski, K., Felicka, E., Śmigielski, J., and Chojnacki, C. (2007). Serum serotonin concentration and urine 5-hydroxyindole acetic acid excretion in patients with irritable bowel syndrome. *Pol Merkur Lek.* **22**: 366--368.

Musil, F., Blaha, V., Ticha, A., Hyspler, R., Haluzik, M., Lesna, J., Smahelova, A., and Sobotka, L. (2015). Effects of body weight reduction on plasma leptin and adiponectin/leptin ratio in obese patients with type 1 diabetes mellitus. *Physiol Res*. **64**: 221--228.

Nakade, M., Akimitsu, O., Wada, K., Krejci, M., Noji, T., Taniwaki, N., Takeuchi, H., and Harada, T. (2012). Can breakfast tryptophan and vitamin B6 intake and morning exposure to

sunlight promote morning-typology in young children aged 2 to 6 years? *J Physiol Anthropol*. **31**:11.

Namkung, J, Kim, H., and Park, S. (2015). Peripheral Serotonin: a New Player in Systemic Energy Homeostasis. *Mol Cells*. **38**: 1023--1028.

Naushad, S. M., Jain, J. M., Prasad, C. K., Naik, U., and Akella, R. R. (2013). Autistic children exhibit distinct plasma amino acid profile. *Indian J Biochem Biophys*. **50**: 474--478.

O'Farrell, K., and Harkin, A. (2017). Stress-related regulation of the kynurenine pathway: Relevance to neuropsychiatric and degenerative disorders. *Neuropharmacology*. **112**: 307--323.

Ogawa, T., Matson, W. R., Beal, M. F., Myers, R. H., Bird, E. D., Milbury, P., and Saso S. (1992). Kynurenine pathway abnormalities in Parkinson's disease. *Neurology*. **42**: 1702--1706.

Oh, C. M., Park, S., and Kim, H. (2016). Serotonin as a New Therapeutic Target for Diabetes Mellitus and Obesity. *Diabetes Metab J*. **40**: 89--98.

Oxenkrug, G. (2013). Insulin resistance and dysregulation of tryptophan-kynurenine and kynurenine-nicotinamide adenine dinucleotide metabolic pathways. *Mol Neurobiol*. **48**: 294--301.

Oxenkrug, G. F. (2015). Increased Plasma Levels of Xanthurenic and Kynurenic Acids in Type 2 Diabetes. *Mol Neurobiol.* **52**: 805--810.

Palego, L., Betti, L., Rossi, A., and Giannaccini, G. (2016). Tryptophan Biochemistry: Structural, Nutritional, Metabolic, and Medical Aspects in Humans. *Journal of Amino Acids*. **2016**: 13.

Patrick, R. P., and Ames, B. N. (2014). Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB Journal*. **28**: 2398--2413.

Porter, R. J., Marshall, E. F., and O'Brien, J. T. (2002). Effects of rapid tryptophan depletion on salivary and plasma cortisol in Alzheimer's disease and the healthy elderly. *J Psychopharmacol*. **16**: 73--78.

Raheja, U. K., Fuchs, D., Giegling, I., Brenner, L. A., Rovner, S. F., Mohyuddin, I., Weghuber, D., Mangge, H., Rujescu, D., and Postolache, T. T. (2015). In psychiatrically healthy individuals, overweight women but not men have lower tryptophan levels. *Pteridines*. **26**: 79--84.

Rambali, B., Van Andel, I., Schenk, E., Wolterink, G., van der Werken, G., Stevenson, H., and Vleeming, W. (2002). The contribution of cocoa additive to cigarette smoking addiction. Bilthoven, The Netherlands: Ministerie van Volksgexondheid, Welzijn en Sport, Rijksinstituut voor Volksgezondheid en Milieu; RIVM Report 650270002/2002.

Reininghaus, E. Z., McIntyre, R. S., Reininghaus, B., Geisler, S., Bengesser, S. A., Lackner, N., Hecht, K., Birner, A., Kattnig, F., Unterweger, R., Kapfhammer, H. P., Zelzer, S., Fuchs, D., and Mangge, H. (2014). Tryptophan breakdown is increased in euthymic overweight individuals with bipolar disorder: a preliminary report. *Bipolar Disord*. **16**: 432--440.

Richard, D. M., Dawes, M. A., Mathias, C. W., Acheson, A., Hill-Kapturczak, N., and Dougherty, D. M. (2009). L-Tryptophan: Basic metabolic functions, behavioral research and therapeutic indications. *Int J Tryptophan Res*. **2**: 45--60.

Ritze, Y., Hengelhaupt, C., Bárdos, G., Ernst, B., Thurnheer, M., D'Haese, J. G., Bischoff, S. C., and Schultes, B. (2015). Altered intestinal neuroendocrine gene expression in humans with obesity. *Obesity (Silver Spring).* **23**: 2278--2285.

Ritze, Y., Schollenberger, A., Hamze Sinno, M., Bühler, N., Böhle, M., Bárdos, G., Sauer, H., Mack, I., Enck, P., Zipfel, S., Meile, T., Königsrainer, A., Kramer, M., and Bischoff, S.C. (2016). Gastric ghrelin, GOAT, leptin, and leptin expression as well as peripheral serotonin are dysregulated in humans with obesity. *Neurogastroenterol Motil*. **28**: 806--815.

Russo, S., Kema, I. P., Bosker, F., Haavik, J., and Korf, J. (2009). Tryptophan as an evolutionarily conserved signal to brain serotonin: molecular evidence and psychiatric implications. *World J Biol Psychiatry*. **10**: 258--268.

Sainio, E. L., Pulkki, K., and Young, S. N. (1996). L-Tryptophan: Biochemical, nutritional and pharmacological aspects. *Amino Acids*. **10**: 21--47.

Savino, F., Liguori, S. A., Benetti, S., Sorrenti, M., Fissore, M. F., and Cordero di Montezemolo, L. (2013). High serum leptin levels in infancy can potentially predict obesity in childhood, especially in formula-fed infants. *Acta Pædiatr*. **102**: 455--459.

Schreiber, W., Schweiger, U., Werner, D., Brunner, G., Tuschl, R. J., Laessle, R. G., Krieg, J. C., Fichter, M. M., and Pirke, K. M. (1991). Circadian pattern of large neutral amino acids, glucose, insulin, and food intake in anorexia nervosa and bulimia nervosa. *Metabolism*. **40**: 503--507.

Schwarcz, R., Bruno, J. P., Muchowski, P. J., and Wu, H. Q. (2012). Kynurenines in the mammalian brain: when physiology meets pathology. *Nat Rev Neurosci*. **13**: 465--477.

Schweiger, U., Warnhoff, M., Pahl, J., and Pirke, K. M. (1986). Effects of carbohydrate and protein meals on plasma large neutral amino acids, glucose, and insulin plasma levels of anorectic patients. *Metabolism*. **35**: 938--943.

Shi, H. L., Liu, C. H., Ding, L. L., Zheng, Y., Fei, X. Y., Lu, L., Zhou, X. M., Yuan, J. Y., and Xie, J.Q. (2015). Alterations in serotonin, transient receptor potential channels and protease-activated receptors in rats with irritable bowel syndrome attenuated by Shugan decoction. *World J Gastroenterol*. **21**: 4852--4863.

Shufflebotham, J., Hood, S., Hendry, J., Hince, D. A., Morris, K., Nutt, D., Probert, C., Potokar, J. (2006). Acute Tryptophan Depletion Alters Gastrointestinal and Anxiety Symptoms in Irritable Bowel Syndrome. *Am J Gastroenterol*. **101**: 2582--2587.

Silva, L. C., Viana, M. B., Andrade, J. S., Souza, M. A., Céspedes, I. C., and D'Almeida, V. (2017). Tryptophan overloading activates brain regions involved with cognition, mood and anxiety. *An Acad Bras Cienc*. **89**: 273--283.

Steinert, R. E., Luscombe-Marsh, N. D., Little, T. J., Standfield, S., Otto, B., Horowitz, M., and Feinle-Bisset, C. (2014). Effects of intraduodenal infusion of L-tryptophan on ad libitum eating, antropyloroduodenal motility, glycemia, insulinemia, and gut peptide secretion in healthy men. *J Clin Endocrinol Metab*. **99**: 3275--3284.

Strasser, B., Berger, K., and Fuchs, D. (2015). Effects of a caloric restriction weight loss diet on tryptophan metabolism and inflammatory biomarkers in overweight adults. *Eur J Nutr*. **54**: 33--42.

Szczepanik, M. (2007). Melatonin and its influence on immune system. *J Physiol Pharmacol*. **58S6**: 115--124.

Tan, L., Yu, J. T., and Tan, L. (2012). The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations. *J Neurol Sci.* **323**: 1--8.

Trupp, M., Jonsson, P., Ohrfelt, A., Zetterberg, H., Obudulu, O., Malm, L., Wuolikainen, A., Linder, J., Moritz, T., Blennow, K., Antti, H., and Forsgren, L. (2014). Metabolite and peptide levels in plasma and CSF differentiating healthy controls from patients with newly diagnosed Parkinson's disease. *J Parkinsons Dis*. **4**: 549--560.

USDA Food Composition Databases. (2017). https://ndb.nal.usda.gov/ndb/nutrients/index

Van Doorn, C., Macht, V. A., Grillo, C. A., and Reagan, L.P. (2017). Leptin resistance and hippocampal behavioral deficits. *Physiol Behav*. **176**: 207--213.

Van Wijngaarden, P., Hadoux, X., Alwan, M., Keel, S., and Dirani, M. (2017). Emerging ocular biomarkers of Alzheimer disease. *Clin Exp Ophthalmol*. **45**: 54--61.

Wada, K., Yata, S., Akimitsu, O., Krejci, M., Noji, T., Nakade, M., Takeuchi, H., and Harada, T. (2013). A tryptophan-rich breakfast and exposure to light with low color temperature at night improve sleep and salivary melatonin level in Japanese students. *J Circadian Rhythms*. **11**: 4.

Wennström, M., Nielsen, H. M., Orhan, F., Londos, E., Minthon, L., and Erhardt, S. (2014). Kynurenic Acid levels in cerebrospinal fluid from patients with Alzheimer's disease or dementia with lewy bodies. *Int J Tryptophan Res.* **7**: 1--7.

Widner, B., Leblhuber, F., and Fuchs, D. (2002). Increased neopterin production and tryptophan degradation in advanced Parkinson's disease. *J Neural Transm (Vienna).* **109**: 181--189.

Widner, B., Leblhuber, F., Walli, J., Tilz, G. P., Demel, U., and Fuchs, D. (1999). Degradation of tryptophan in neurodegenerative disorders. *Adv Exp Med Biol*. **467**: 133--138.

Widner, B., Leblhuber, F., Walli, J., Tilz, G. P., Demel, U., and Fuchs, D. (2000). Tryptophan degradation and immune activation in Alzheimer's disease. *J Neural Transm (Vienna).* **107**: 343--353.

Winkler, L. A., Frølich, J. S., Gudex, C., Hørder, K., Bilenberg, N., and Støving, R. K. (2016). Patient- and clinician- reported outcome in eating disorders. *Psychiatry Res.* **30**: 230--235.

Wissmann, P., Geisler, S., Leblhuber, F., and Fuchs, D. (2013). Immune activation in patients with Alzheimer's disease is associated with high serum phenylalanine concentrations. *J Neurol Sci.* **329**: 29--33.

Wollny, T., Rydzewska, G., Pawlak, D., Turecka-Kulesza, E., Buczko, W., and Łaszewicz, W. (2006). Kynurenic pathway metabolites in serum of patients with irritable bowel syndrome – possible role in the mechanism of visceral pain. *Gastroenterologia Polska*, **13**: 159–162.

Wurtman, R. J., and Wurtman, J. J. (1995). Brain serotonin, carbohydrate-craving, obesity and depression. *Obes Res.* **3**: 477--480.

Youssef, M. (2015). The effect of dietary intervention by low carbohydrate diet, and low fat diet, on weight loss, leptin and adiponectin. *Life Sci J.* **12**: 33--42.

Yu, E., Ruiz-Canela, M., Guasch-Ferré, M., Zheng, Y., Toledo, E., Clish, C.B., Salas-Salvadó, J., Liang, L., Wang, D. D., Corella, D., Fitó, M., Gómez-Gracia, E., Lapetra, J., Estruch, R., Ros, E., Cofán, M., Arós, F., Romaguera, D., Serra-Majem, L., Sorlí, J. V., Hu, F. B., and Martinez-Gonzalez, M. A. (2017). Increases in plasma tryptophan are inversely associated with incident cardiovascular disease in the Prevención con dieta Mediterránea (PREDIMED) Study. *J Nutr.* **147**: 314--322.

Zablotsky, B., Black, L. I., Maenner, M. J., Schieve, L. A., and Blumberg, S. J. (2015). Estimated prevalence of autism and other developmental disabilities following questionnaire changes in the 2014 National Health Interview Survey. *Natl Health Stat Report.* **87**: 1–20.

Żelowski, A., Wojtuń, S., Gil, J., and Dyrla, P. (2013). Irritable bowel syndrome – diagnostics and treatment principles. *Pediatria i Medycyna Rodzinna*. **9**: 250--255.

Zhang, C., Yin, A., Li, H., Wang, R., Wu, G., Shen, J., Zhang, M., Wang, L., Hou, Y., Ouyang, H., Zhang, Y., Zheng, Y., Wang, J., Lv, X., Wang, Y., Zhang, F., Zeng, B., Li, W., Yan, F., Zhao, Y., Pang, X., Zhang, X., Fu, H., Chen, F., Zhao, N., Hamaker, B. R., Bridgewater, L. C., Weinkove, D., Clement, K., Dore, J., Holmes, E., Xiao, H., Zhao, G., Yang, S., Bork, P., Nicholson, J. K., Wei, H., Tang, H., Zhang, X., and Zhao, L. (2015). Dietary modulation of gut microbiota contributes to alleviation of both genetic and simple obesity in children. *EbioMedicine*. **2**: 968--984.

Zhou, T., Shimabukuro, M., Koyama, K., Lee, Y., Wang, M. Y., Trieu, F., Newgard, C. B., and Unger, R. H. (1997). Induction by leptin of uncoupling protein-2 and enzymes of fatty acid oxidation. *Proc Natl Acad Sci U S A.* **94**: 6386--6390.

Table 1. Tryptophan amount per 100 g in common foods.

	Tryptophan (mg)
milk	42
eggs	165
wheat flour	110
sausage	93
potato	28
chees	325
beef	230
banana	10
soybeans	160
bread, oat bran, toasted	140
chia seeds, dried	440
chicken, breast, skinless, boneless, meat only	400
cocoa	290

Table 2. Summary of studies regarding amount of tryptophan and its metabolites in body fluids in various diseases or disorders.

No.	Disease or disorder	Metabolites	Study population	Sex	Sample	Relation to disease	Level of metabolite	Methods	Reference
1	Irritable Bowel Syndrome (IBS)	kynurenine (Kyn) tryptophan (Trp) IFN-γ	41 IBS 33 controls	female	plasma	Increase of Trp along the Kyn catabolic pathway caused increased sensivity of the IDO to IFN-γ and association between IFN-γ and Kyn/Trp ratio contribute to serotonergic dysfunction, via deficit 5-HT, which may explain generation gastrointestinal symptom and increase incidence of anxiety and depression.	Kyn ↑ Trp ↔ Kyn/Trp ↑ IFN-γ ↔	Trp, Kyn- HPLC IFN-γ- electrochemiluminescence multiplex system	Fitzgerald et al., 2008
2	Irritable Bowel Syndrome (IBS)	kynurenic acid (KYNA) quinolinic acid (QA)	37 IBS 20 controls	both	serum	Control of the gut motility and enteric neurnal excitability is involved balance between quinolinic and kynurenic acid.	KYNA ↓ QA ↑	HPLC	Wollny et al., 2006
3	Irritable Bowel Syndrome (IBS)	tryptophan (Trp) serotonin (5-HT) 5-hydroxyindoloacetic acid (5-HIAA)	14 IBS 14 controls	both	plasma	Serotonergic modulation by ATD[a] affects visceral perception and cognition in IBS and control.	Trp ↓ 5-HIAA↓	HPLC	Kilkens et al., 2004
4	Irritable Bowel Syndrome (IBS)	serotonin (5-HT) 5-hydroxyindoloacetic acid (5-HIAA)	23 IBS-C 23 IBS-D 25 controls	both	serum urine	Metabolism of 5-HT and secretion may be disturbed in irritable bowel syndrome (IBS). Disturbed metabolism of serotonin probably play a role in pathogenesis of functional bowel diseases.	5-HT ↑ 5-HIAA↓	ELISA	Moskwa et al., 2007
5	Irritable Bowel Syndrome (IBS)	tryptophan (Trp)	8 IBS-C 10 IBS-D 11 control	both	plasma	Rise level of tryptophan affects on gastrointestinal symptoms in IBS and also decreases anxiety symptoms.	ATD[a]: Trp ↓ ATI[b]: Trp ↓	HPLC	Shufflebotham et al., 2006

6	Irritable Bowel Syndrome (IBS)	serotonin (5-HT)	29 IBS-C 55 IBS-D 35 controls	both	plasma	Modulating of different 5-HT receptors are involving in IBS. Reduced 5-HT reuptake connected with IBS-D, impaired release may be linked with IBS-C.	IBS:C: 5-HT ↓ IBS-D: 5-HT ↑	HPLC	Atkinson et al., 2006
7	IBS-D	serotonin (5-HT)	39 IBS-D 20 controls	femal e	plasma	Symptom exacerbation following meal ingestion in patients with IBS-D is connected with increased levels of plasma 5-HT, together with a reduction in 5-HT turnover.	5-HT ↑	HPLC	Houghton et al., 2003
8	Irritable Bowel Syndrome (IBS)	serotonin (5-HT) 5-hydroxyindoloacetic acid (5-HIAA)	15 IBS-C 15 IBS-D 15 controls	both	plasma	IBS-C patients show impaired postprandial 5-HT release.	IBS-C: 5-HT ↑ 5-HIAA ↓	HPLC	Dunlop et al., 2005
9	Chronic Kidney Disease (CKD)	tryptophan (Trp) 10 metabolites of Trp[c]	27	both	serum	Decline in kidney function is associated with metabolism of tryptophan via the kynurenine pathway, without evident elimination of tryptophan metabolism via the 5-HT pathway.	KYNA ↑ were associated with ↓ cognitive function IAA ↑ was correlated with anxiety and depression	LC-MS/MS	Karu et al., 2016
10	Obesity	tryptophan (Trp) Trp /LNAA[d] ratio	9 obese 8 controls	both	plasma	Brain Trp uptake is correlated with the plasma Trp/LNAA ratio. This determine brain serotonin synthesis. Serotonin-mediated regulation of food intake may contribute to blunted Trp/LNAA, which response to carbohydrate intake in the obese.	Trp ↓	HPLC	Caballero et al., 1998
11	Obesity	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	359 ow/ob[e] 212 controls	both	serum	Induction of the Trp-Kyn pathway are associated to development of the metabolic syndrome in obesity. Obesity and Trp metabolism differs between juveniles and	adult: Trp ↓ Kyn ↑ Kyn/Trp ↑ juvenile: Trp ↑ Kyn ↓ Kyn/Trp ↓	HPLC	Mangge et al., 2014

						adults.					
12	Obesity	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	27 overweigh t 11 obese	both	serum	Disturbed metabolism of Trp influents on biosynthesis of serotonin and might be associated with increased carbohydrate craving and susceptibility for mood disturbances.		VLCD[f]	LCD[g]	HPLC	Strasser et al., 2015
							Trp	↓	↓		
							Kyn	↓	↓		
							Kyn/Trp	↔	↔		
13	Obesity/Depressio n	tryptophan (Trp)	973 individuals	both	plasma	Lower Trp levels in overweight/obese woman suggests that low Trp (low serotonin synthesis) may contribute to either vulnerability to depression in obese women or vulnerability to obesity in depressed women.	ow /ob[e]	wome n	men	HPLC	Raheja et al., 2015
							Trp	↓	↑		
14	Type 2 Diabetes (T2D)	tryptophan (Trp) kynurenine (Kyn) kynurenic acid (KYNA)	30 T2D 24 controls	both	plasma	Increased plasma levels of Kyn and KYNA of T2D patients might confirm "kynurenine hypothesis'' of insulin resistance and its progression to T2D.	Trp ↑ Kyn ↑ KYNA ↑			GC-MS	Oxenkrug, 2015
15	Bipolar Disorder (BD)	kynurenine (Kyn) Kyn/Trp ratio	78 BD (54 overweigh t, 24 normal weight), 156 controls (76 overweigh t, 80 normal weight)	both	serum	Increased level of kynurenine and Kyn/Trp ratio in the overweight patients with BD could be connected between short periods of euthymia and worsening of illness course in overweight patients with BD.	Overweight patients with BD: Kyn ↑ Kyn/Trp ↑			HPLC	Reininghaus et al., 2014
16	Anorexia Nervosa (AN)	tryptophan (Trp)	32 acAN[h] 32 recAN[i] 32 controls	femal e	plasma	In acAN[h] patients observed lower Trp levels, which also influence in diminished 5-HT. Reduced availability of the 5-HT may account for the poor response to treatment AN patients.		acAN[h]	recAN[i]	HPLC	Ehrlich et al., 2009
							Trp	↓	↓		

17	Anorexia Nervosa (AN)	5-hydroxyindoloacetic acid (5-HIAA)	14 AN 10 controls	female	cerebrospinal fluid (CSF)	Central nervous system serotoninergic metabolism is associated with weight loss and malnutrition in AN.	5-HIAA ↓	GC-MS	Kaye et al., 1988
18	Anorexia Nervosa (AN)	tryptophan (Trp) serotonin (5-HT) LNAA[d] Trp/LNAA ratio	42 AN 42 controls	both	plasma	Decrease in depressive symptoms and anxiety, which encountered in the course of re-feeding in AN may be bio-availability of tryptophan.	Trp ↓ 5-HT ↓ LNAA[d] ↓ Trp/LNAA ↓	HPLC	Gauthier et al., 2014
19	Anorexia Nervosa (AN)	tryptophan (Trp) LNAA[d] Trp/LNAA ratio	13 AN 21 controls	female	plasma	Mood disturbances have been connected with reduce serotonergic function. In AN individuals observed reduced central serotonin metabolism (brain tryptophan availability decreased).	Trp: after protein meal ↑ after carbohydrate meal ↓ Trp/LNAA: after protein meal ↓ after carbohydrates meal ↑	HPLC	Schweiger et al., 1986
20	Bulimia (BN) and Anorexia Nervosa (AN)	tryptophan (Trp) LNAA[d] Trp/LNAA ratio	13 BN 10 AN 15 controls	female	plasma	Decreased Trp/LNAA ratio may cause consequences such as disturbances of mood and neuroendocrine regulation in AN individuals.	AN: Trp/LNAA ↓ vs control BN: Trp/LNAA ratio ↔ vs controls	HPLC	Schreiber et al., 1991
21	Anorexia Nervosa (AN)	tryptophan (Trp) serotonin (5-HT) Trp/LNAA ratio	19 AN 12 controls	both	blood	In pathology could be involved all measured biological indices except 5-HT. AN is associated with impulsivity and anxiety.	5-HT ↑ total Trp ↓ free Trp ↓ total Trp/LNAA ↓	HPLC	Askenazy et al., 1998
22	Anorexia Nervosa (AN)	tryptophan (Trp) serotonin (5-HT) 5-hydroxytryptophan (5-HTP)	16 AN 25 controls	female	serum	Based on these studies can be distinguished two different subgroups of AN patients. One of group characterized by a markedly lower Trp level and higher levels of 5-HTP and 5-HT.	Trp ↓ 5-HT ↓ 5-HTP ↑	HPLC	Comai et al., 2010

23	Anorexia Nervosa (AN)	tryptophan (Trp)	20 AN 20 controls	-	serum	High level of Trp may trigger AN because Trp is a precursor of 5-HT. Serotonin is responsible for mood regulation, and it high level may cause depression and decreased eating which leads to AN.	Trp ↑	HPLC	Naureen et al., 2014
24	Bulimia Nervosa (BN)	tryptophan (Trp) Trp/LNAA ratio	22 BN 16 controls	femal e	plasma	Participants with BN can be more vulnerable to the mood lowering effects of ATD[a]. Acute changes in 5-HT activity are linked with mood BN subjects.	Trp ↑	fluorometric method of Denkla and Dewey	Kaye et al., 2000
25	Autism (ASD)	tryptophan (Trp)	37 ASD 28 controls adults 12 controls child	-	plasma	Abnormal Trp-serotonin metabolism in the brain might be responsible for the clinical manifestations and behavioral abnormalities of autism. High free Trp level is responsible for lower mental development and hyperactivity.	total Trp ↔ free Trp ↑	fluorometric method of Denkla and Dewey	Hoshino et al., 1986
26	Autism (ASD)	tryptophan (Trp)	20 ASD adults	both	plasma	Changes in behavior (increasing whirling, banging, hitting self, rocking, and toe walking) are triggered by depleting Trp in adult patients with ASD.	-	HPLC	McDougle et al., 1996
27	Autism (ASD)	tryptophan (Trp)	55 ASD children 44 controls	both	plasma	Decrease level of Trp in ASD could impair serotonin synthesis, and this lead to a worsening in behavior in ASD subjects. Lower level of Trp might be due to reduced protein intake and/or dysfunction in synthesizing protein into amino acids in the digestive tract.	Trp ↓	HPLC-MS/MS	Adams et al., 2011

28	Autism (ASD)	tryptophan (Trp)	138 ASD children 138 controls	both	plasma	Lower level of Trp may deterioration in the behavior of autistic children. Trp and other LNAA[d] compete for brain serotonin synthesis and when is low level of Trp then is low brain serotonin synthesis.	Trp ↓	HPLC	Naushad et al., 2013
29	Autism (ASD)	tryptophan (Trp)	33 ASD children 21 controls	both	urine	Abnormal Trp-serotonin metabolism in the brain might be responsible for the worsening of autistic symptoms. Reduce level of Trp may cause increased irritability and mild depression.	Trp ↓	GC-MS	Kałużna-Czaplińska et al., 2010
30	Autism (ASD)	tryptophan (Trp)	14 ASD children 10 controls	both	urine	Lower level of Trp may lead to the worsening of autistic symptoms (increased irritability and mild depression).	Trp ↓	GC-MS	Kałużna-Czaplińska et al., 2014
31	Autism (ASD)	tryptophan (Trp)	48 ASD 53 controls	both	urine	Abnormal amino acid metabolism (including Trp metabolism), increased oxidative stress, and altered gut microbiomes in ASD.	Trp ↓	UPLC/MS/MS GC-MS	Ming et al., 2012
32	Parkinson's Disease (PD)	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	22 PD 11 controls	both	serum, cerebrospinal fluid (CSF)	Increased Trp degradation in peripheral blood in PD patients substantiates that in this disease participate immunological abnormalities. Interferon-mediated IDO activity is responsible for the increased Trp degradation rate as is evident by the increased Kyn/Trp ratios.	Trp ↓ Kyn ↓ Kyn/Trp ↑	HPLC	Winder et al., 2002
33	Parkinson's Disease (PD)	tryptophan (Trp)	20 PD 20 controls	both	cerebrospinal fluid (CSF)	Degradation of Trp can lead to the generation of 3-HKA, a compound leading to	Trp ↓	GC-TOFMS	Trupp et al., 2014

						increased oxidative stress in preclinical PD studies.			
34	Parkinson's Disease (PD)	3-hydroxykynurenine (3-HK)	48 PD 57 controls	-	cerebrospinal fluid (CSF)	3-HK linked with potent excitotoxicity properties. Block production of 3-HK (through Trp catabolism) allows neuroprotective strategy and therapeutic intervention against 3-HK formation.	3-HK ↑	UHPLC-MS/MS GC-MS	Lewitt et al., 2013
35	Parkinson's Disease (PD)	tryptophan (Trp)	92 PD 65 controls	both	urine	Degradation of Trp may be connected with the activated cell-mediated immune response typical of PD.	Trp ↓	GC-MS LC-MS	Luan et al., 2015
36	Alzheimer's Disease (AD)	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	21 AD 20 controls	-	serum	Increased Trp degradation in AD patients is associated with signs of a chronic immune activation, while increased Kyn/Trp was associated with reduced cognitive performance.	Trp ↓ Kyn ↑ Kyn/Trp ↑	HPLC	Widner et al., 1999
37	Alzheimer's Disease (AD), Huntington's disease (HD)	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	24 AD 12 HD	-	serum	Systemic chronic immune activation in patients with AD and HD is associated with significant degradation of Trp, which is most likely due to activation of IDO by immunologic stimuli.	Trp ↓ Kyn ↓ Kyn/Trp ↑	HPLC	Widner et al., 2000
38	Alzheimer's Disease (AD)	tryptophan (Trp) kynurenine (Kyn) Kyn/Trp ratio	43 AD	both	serum	Increased blood concentration of Kyn/Trp is associated with immune activation and inflammation represent critical factors in the pathogenesis of AD.	Trp ↓ Kyn ↑ Kyn/Trp ↑	HPLC	Wissmann et al., 2013
39	Alzheimer's Disease (AD)	tryptophan (Trp)	16 AD 17 controls	both	plasma	Acute Trp depletion had no effect on cortisol secretion for subjects with AD and healthy	Trp ↓	HPLC	Porter et al., 2002

						controls.			
40	Alzheimer's Disease (AD)	kynurenic acid (KYNA)	19 AD 20 controls	both	cerebrospinal fluid (CSF)	No significant alterations in CSF KYNA levels in AD patients compared to controls. In AD the inconsistency of KYNA alterations could be because of the heterogeneity of the disease.	KYNA ↔ KYNA ↑ female AD vs male AD	HPLC	Wennström et al., 2014
41	Sleep Disorders (SD)	melatonin	94 individuals	male	saliva	The combined intervention on breakfast, morning sunlight and evening-lighting seems to be effective to keep higher melatonin secretion at night. Higher level of melatonin is responsible for easy onset of the night sleep and higher quality of sleep.	melatonin ↑ in G3 vs G1 and G2[j]	ELISA	Wada et al., 2013
42	Delayed Sleep Phase Syndrome (DSPS)	melatonin	56 individuals	both	saliva	Examination of the melatonin secretion profile can reveal several key differences between individuals with and without circadian rhythm disruptions.	The time of melatonin secretion are significantly delayed in DSPS patients.	ELISA	Rahman et al., 2009
43	Sleep Deprivation	tryptophan (Trp) serotonin (5-HT)	109 individuals	-	plasma	The increased levels of 5-HT and Trp may explain the antidepressive effect of acute sleep deprivation.	Trp ↑ 5-HT ↑	LC-MS	Davies et al., 2014

↔ no differences in levels metabolite between subjects with disease/disorder and controls

↑ increase level of metabolite in subjects with disease/disorder compared to controls

↓ decrease level of metabolite in subjects with disease/disorder compared to controls

[a] ATD- Acute Tryptophan Depletion

[b] ATI- Acuter Tryptophan Increase, subjects consumed an amino acid drink that either containing 2.3 g Trp

[c] 10 metabolites of Trp:

serotonin (5-HT)

5-hydroxy-3-indole acetic acid (5-OH IAA)

kynurenine (Kyn)

kynurenic acid (KYNA)

quinolinic acid

xanthurenic acid

quinaldic acid

3-OH anthranilic acid

indoxyl sulfate

indole-3-acetic acid (IAA)

[d]LNAA- Large Neutral Amino Acids

[e]ow/ob- overweight/obese subjects

[f]VLCD- Very Low Caloric Diet

[g]LCD- Low Caloric Diet

[h]acAN- participants with acute anorexia nervosa (AN)

[i]recAN- participants were previously treated for anorexia nervosa (AN)

[j]G1- no intervention

G2- have protein-rich foods and vitamin B-6-rich foods at breakfast and sunlight exposure after breakfast

G3- the same content as G2 and incandescent light exposure at night

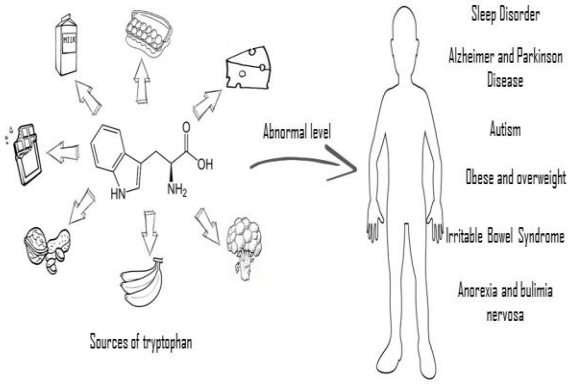

Figure 1. Tryptophan and different diseases.

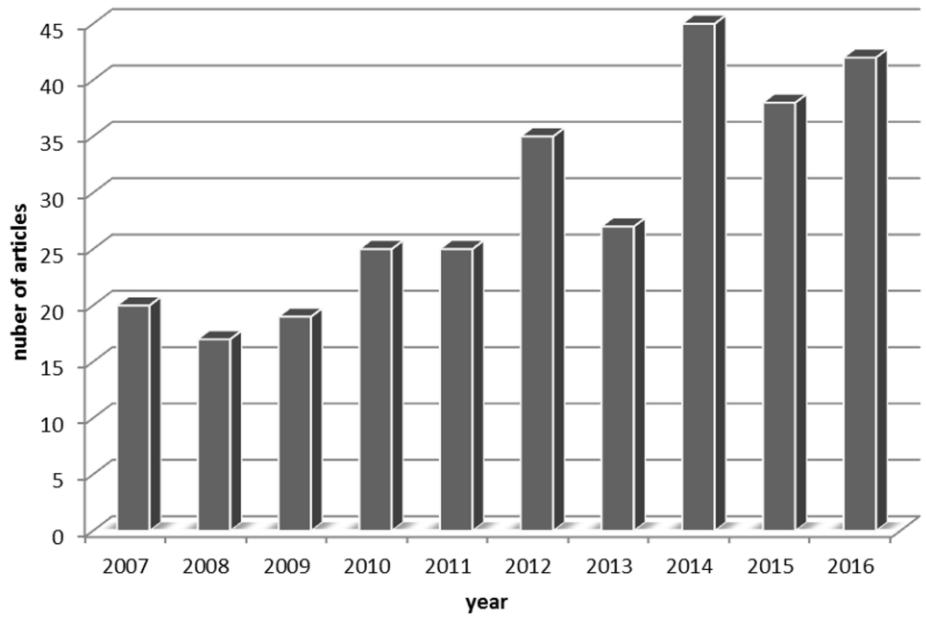

Figure 2. Diagram of the frequency of scientific reports on the use of tryptophan supplementation in the study of different diseases in 2007--2016. The literature review was based on PubMed sources, sorted by best match, for the phrase: tryptophan supplementation or Trp supplementation and diseases.