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CURRENT OPINION

Tryptophan: 'essential' for the pathogenesis of irritable bowel syndrome?

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Introduction

Tryptophan is an 'essential' amino acid: humans cannot make it themselves, but must obtain it in the form of food. In addition to being a building block in the biosynthesis of proteins, this aromatic substance can be converted into a number of metabolites of great clinical importance. The best known is the enzymatic conversion to serotonin. However, in recent years, attention has increasingly focused on the medical significance of the enzymatic oxidation of tryptophan to form indole compounds collectively known as kynurenines. Both excessive kynurenine production and an accompanying deficiency of the substrate, tryptophan, may be the cause of a number of pathological conditions. In addition, the oxidation itself may affect the body's redox balance. In this article, we hypothesize that tryptophan is 'essential' in the pathogenesis of irritable bowel syndrome (IBS).

Indolamine dioxygenase

Indolamine dioxygenase (IDO) is the key enzyme involved in the conversion of tryptophan in the intestine. The enzyme catalyses oxidation of tryptophan to kynurenine in a reaction that produces peroxide and gives rise to highly reactive and potentially harmful oxygen and hydroxyl radicals. The IDO reaction may therefore contribute to what is generally called oxidative stress [1,2]. Oxygen and hydroxyl radicals formed as a result of the IDO reaction will accelerate the oxidation of nitrogen monoxide (NO) to nitrite (NO_2) and of ferrous iron compounds to ferric iron compounds. The reactive oxygen products have an antimicrobial effect, but may also harm mitochondria and lead to increased production of inflammatory cytokines (TNF-α, IL-6) [3,4] and be causally related to fatigue and pain hypersensitivity [5,6].

The harmful effects of the IDO reaction may be counteracted by ascorbic acid (vitamin C) and by antioxidants that occur naturally in plants. Most antioxidants in plants are members of the main groups polyphenols, carotenoids and flavonoids. The best known are curcumin in turmeric, catechines in green tea, resveratrol in red wine and epigallocatechins in cocoa. In addition to phenol antioxidants, edible plants in the *Brassica* family, such as cabbage and broccoli, contain glucosinolates that are broken down in the stomach to thiocyanates. These compounds help to control the redox balance in the intestine, for example, by activating the redox-regulating transcription factor Nrf2 [7]. Glucosinolates also give rise to indole products that are identical to some of those formed by enzymatic breakdown of tryptophan in the intestine, for example, indole-3-carbinol and 3,3-di-indolylmethane [7].

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Hypothesis

Increased production of peroxide and reactive oxygen as a result of IDO activation may conceivably disrupt the finely tuned interaction between oxidants and antioxidants, concurrently with a change in the tryptophan and kynurenine levels. Perhaps such disruptions in the redox and tryptophan–kynurenine balance, and alterations in levels of tryptophan and tryptophan metabolites can 'explain' the abdominal and systemic symptoms of IBS? If this is the case, tryptophan is indeed essential, also in IBS pathogenesis.

The kynurenine pathway

Up to the present, interest in tryptophan from a medical perspective has focused mainly on its role in serotonin metabolism. Serotonin is an important neurotransmitter in the enteric and central nervous system. In the bowel, it regulates secretion, motility and sensibility, while in the central nervous system it modulates mood, cognition and sleep. Neuropsychiatric problems have been attributed to too much or too little serotonin. For example, it has been demonstrated that a temporary tryptophan deficiency causes memory failure in healthy individuals [8]. In recent years, the focus has been more on tryptophan metabolism via kynurenine (the kynurenine pathway), where most of the tryptophan is catabolised by the IDO in the gastrointestinal tract. Tryptophan 'surplus' is catabolised in the liver, but by a different dioxygenase from IDO: tryptophan-2,3-dioxygenase. Only 1% of tryptophan intake is metabolised into serotonin, and the two metabolic pathways (serotonin and kynurenine) compete for the substrate (tryptophan) [9]. Increased consumption of tryptophan via the kynurenine pathway may result in too little tryptophan and serotonin in both the central nervous system and the gastrointestinal tract. It has been clearly shown to cause symptoms of anxiety and low mood in mice [10]. This may also be relevant for humans, because people vulnerable to stress may benefit from tryptophan supplements, for example, in the form of tryptophan-rich albumin or whey protein hydrolysates [11].

Most of the serotonin in the body (95%) is found to be in the gastrointestinal tract. Interestingly, studies have demonstrated that patients with IBS have low serotonin concentrations [12] and small numbers of serotonin-containing neuroendocrine cells in the small intestine [13]. Acting on mucosal and submucosal neurons in a paracrine fashion, serotonin is highly important for regulation of motility of the gastrointestinal tract. Impaired small intestinal motor function, as observed in patients with IBS [14], may thus be a consequence of too low serotonin levels within the intestinal wall. The end product of serotonin catabolism, 5-hydroxy indole acetic acid, is excreted in urine. In patients with IBS this excretion is low, indicating low production of serotonin as well [15]. Serotonin is inactivated by reuptake to enterocytes, neurons and platelets, and this serotonin transport function is reduced in patients with IBS, possibly a result of increased production of interferon gamma (INFγ) [16,17].

Immunoactivation that results in increased production of INFγ will also increase IDO activity [1]. IDO oxidation stimulated by tryptophan has proved to be of great significance for such diverse diseases as myocardial infarction, Alzheimer's disease and mental retardation [8,18,19], and tryptophan is used in some therapeutic combinations for cognitive impairment in the elderly [20]. Activation of the kynurenine pathway also has an immunomodulatory effect, and is of significance for the development of multiple allergies and autoimmune diseases [21,22]. Both local tryptophan deficiency and systemic metabolites from the kynurenine pathway are considered to play an important part in this interaction. Thus, local tryptophan depletion in and around infected mucosal cells may impair microbial growth [23]. Intestinal malabsorption may also contribute. Patients with IBS and chronic fatigue often have signs of low-grade malabsorption with deficiencies of iron, vitamin B12, folic acid and vitamin D, and we have previously demonstrated that about 30% of IBS patients have fat malabsorption [24]. Ledochowski et al. demonstrated as early as in 2001 that an excessively high fructose level in the colon may reduce the availability of tryptophan as a substrate for biosynthesis of serotonin, and that serotonin deficiency and depression may be associated with fructose malabsorption [25].

Microbial IDO activation?

A high kynurenine/tryptophan ratio is the result of a high level of activity in the kynurenine pathway, and this may be the closest one comes to a biomarker for IBS [26,27]. But this ratio is also high in a number of other inflammatory conditions and types of cancer where there is a high INFγ, either locally or systemically [26,28]. Low tryptophan and a high kynurenine/tryptophan ratio are therefore not specific to IBS, but may indicate an underlying low-grade inflammatory process. This immunoactivation and subsequent high IDO activity may conceivably have a microbial cause. Brottveit et al. recently described an INFγ increase in

duodenal biopsies after intake of gluten-containing bread by gluten-sensitive patients without coeliac disease [29]. The mechanisms and consequences of this INFγ increase have not been determined. Gluten is only partly digestible by human enzymes, and remains semi-digested and unabsorbed in the small intestine. Undigested gluten peptides may be directly toxic [30], antimicrobial and immunomodulatory [31]. INFγ activation is an important part of the innate immune system and may be induced by microbes [32,33]. As soon as the undigested gluten peptides reach the large intestine, they become food for the intestinal bacteria [34], and the question is whether it is this gluten-stimulated intestinal flora that causes IBS-like symptoms in patients with non-coeliac gluten-sensitivity. Our hypothesis is that INFγ activation and subsequent IDO oxidation of tryptophan is a pathogenetic mechanism of IBS and that the initial stimulus may be of microbial origin also in the case of non-coeliac gluten-sensitivity.

Does tryptophan act via aryl hydrocarbon receptor?

The receptor protein aryl hydrocarbon receptor (AhR) has been preserved in phylogenesis of vertebrates for several hundred million years. It used to be believed that its primary significance was in the inactivation of environmental toxins such as xenobiotics, by stimulating the activity of cytochrome P (CYP) enzymes. However, activated AhR also functions as an intracellular transcription factor that governs a number of vital functions [35] and is necessary *inter alia* for normal intestinal immune function. Of particular interest to us is the fact that AhR regulates the barrier function of the intestinal mucous membrane, apparently in a system whereby the mucous membrane 'tastes' the contents of the intestine and regulates its defences accordingly. AhR activation of lymphoid cells produces cytokines (IL-22), which regulate the immune system and development of tolerance. These innate lymphoid cells (ILC) form part of the innate immune system. In other words, the 'old' receptor (AhR) acts on cells that are ready to function already at birth, and we are clearly dealing with an innate immune system here. A number of studies have revealed that AhR ligands regulate the number of intraepithelial and regulatory T cells, cytotoxic T cells, antibody-producing B cells and mast cells. Failure of this immune system may result in autoimmunity and allergy [36].

Since AhR is an innate receptor in a number of cells, it is reasonable to assume that endogenous ligands may exist – and they do. New AhR ligands are constantly being found, and many of them actually prove to be tryptophan metabolites [37]. INFγ-induced tryptophan degradation may induce antimicrobial and immunomodulatory effects in epithelial cells [31]. Little research has been conducted on the importance of the intestinal flora in this regard, but the microbes can metabolise tryptophan and give rise to AhR ligands, which in turn affect the mucous membrane defence. The lactic acid bacteria (i.e., *Lactobacillus reuteri* in the intestine and *L. acidophilus* in the vagina) eat tryptophan as a source of energy and produce indole-3-aldehyde (IAld), an AhR ligand that activates ILC and releases IL-22, which stimulates the production of antimicrobial peptides, curbs the growth of *Candida albicans*, but boosts the growth of lactic acid bacteria. Given the choice, bacteria eat sugar rather than amino acids – and without tryptophan in their 'diet' they do not produce IAld – which will mean less lactobacilli and more *Candida* [33], which is typical of IBS.

It was also shown recently that kynurenine activates mast cells via AhR [38] and that AhR is upregulated in allergic rhinitis [39] and can be inhibited by another (non-toxic) tryptophan metabolite (abbreviated to ITE) [40]. These metabolites present very interesting possibilities for developing new treatments for allergies. However, there are a number of AhR ligands that are much more readily available and that may be equally interesting: the *Brassica* family, for example, contains tryptophan derivatives (glucosinolates) which convert gastric acid into potent AhR ligands that contribute to a favourable microbial environment in the stomach [41]. A relevant question is therefore: How much and in what manner is this regulatory system affected by our daily diet?

Therapeutic possibilities for IBS

If IBS and associated health problems like fibromyalgia and fatigue [42] are an IDO-stimulated consequence of an abnormal intestinal flora, one might imagine that the problems could be treated with antibiotics. Interestingly, we sometimes see astonishing results due to antibiotics, but in our experience, unfortunately, the patients subsequently become sicker than ever. We suspect that the guilty microbes are facultative anaerobes, and that they are mucous-producing and possibly 'conceal themselves' in a biofilm of mucus [43]. Lipopolysaccharide (LPS) from Gram-negative bacteria may stimulate IDO [44], but LPS and CD14 in blood appear to be normal (unpublished data), even though the LPS receptor TLR4 may appear upregulated in the colon of a subgroup of IBS patients [45]. We therefore

believe that the undesirable intestinal flora is not Gram-negative.

When antibiotics do not work, we must find other options. Dietary treatment (low FODMAP diet) to 'starve' the bacteria has proved useful [46], but hardly curative. The alternative, bacteriotherapy, is increasingly in fashion. Following the publication of a study of such therapy for patients with post-giardiasis IBS [47], we have noticed great interest in faecal bacteriotherapy (a variant of faecal microbiota transplantations). The effect was transitory, unfortunately, but perhaps better, nonetheless, than the effect of rifaximin, a non-absorbable antibiotic that was recently described in the *New England Journal of Medicine* [48]. However, getting the installed flora to establish themselves in a new host is a major problem that may be due to changes in the environment of the host's 'fermentation chamber' – the coecum. The contents of the coecum should normally be slightly acidic, with a pH of between 5 and 6, and the acidity in the coecum is related to the redox potential [49]. If the redox potential is not low enough (not sufficiently anoxic), there will be excessive growth of facultative anaerobic bacteria, and the fermentation process will be incomplete [50]. With too high oxygen tension in the coecum, reactive oxygen species will be generated, which can oxidise NO to NO_2 leaving an NO deficiency, while NO_2 (and other oxidation products) may become 'food' for a non-benign bacterial flora [51]. If the host coecum does not have the correct redox potential, this may be sufficient to prevent new flora establishing themselves – until something is first done with the host redox environment. This is a challenge that has not yet been solved.

Exogenic addition of tryptophan may increase levels of serotonin and benign AhR ligands. However, this gives rise to the fear that one may be 'adding fuel to the flames,' because tryptophan oxidation will give rise to more reactive oxygen compounds. This is where the combination with antioxidants comes in. If we can curb the oxidative stress with antioxidants, the favourable effects of increased levels of serotonin and AhR ligands may make the overall effect of administering tryptophan positive. Thiocyanates formed by the breakdown in the stomach of glucosinolates in *Brassica* plants may be of special interest because they activate the Nrf2 receptor and have a regulatory effect on the redox level [7]. A diet high in *Brassica* vegetables is associated with reduced risk of chronic diseases [7], and constitutes an uninvestigated possibility of reducing pain and pain hypersensitivity in IBS and fibromyalgia [5,6]. In the past, we probably consumed much larger quantities than we do now, because hybridisation of *Brassica* plants has led to a reduction in their glucosinolate levels [52].

Concluding remarks

IBS may be related to disrupted tryptophan metabolism with increased oxidative stress and deficiencies of tryptophan and tryptophan-derived AhR ligands [36]. The cause may be dysbiosis [53] due to high intake of carbohydrates [46]. If the microbes get their preferred food (sugar), they do not produce AhR ligands that strengthen the defences of and barrier presented by the mucous membranes. Without these AhR ligands, the ratio between the lactic acid bacteria and *C. albicans* is reduced and the immunobalance skewed in favour of the development of IBS, allergies and autoimmune diseases. When we say 'You AhR what you eat' [54], it means that a number of disorders, including IBS, fibromyalgia and fatigue, may be indirect consequences of diet, mediated by the essential amino acid tryptophan and its microbial metabolites. So perhaps it is more correct to say 'You AhR what your microbiota eat?'

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