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POSSIBLE LINKS BETWEEN INTESTINAL PERMEABLITY AND FOOD PROCESSING: A POTENTIAL THERAPEUTIC NICHE FOR GLUTAMINE

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Increased intestinal permeability is a likely cause of various pathologies, such as allergies and metabolic or even cardiovascular disturbances. Intestinal permeability is found in many severe clinical situations and in common disorders such as irritable bowel syndrome. In these conditions, substances that are normally unable to cross the epithelial barrier gain access to the systemic circulation. To illustrate the potential harmfulness of leaky gut, we present an argument based on examples linked to protein or lipid glycation induced by modern food processing. Increased intestinal permeability should be largely improved by dietary addition of compounds, such as glutamine or curcumin, which both have the mechanistic potential to inhibit the inflammation and oxidative stress linked to tight junction opening. This brief review aims to increase physician awareness of this common, albeit largely unrecognized, pathology, which may be easily prevented or improved by means of simple nutritional changes.

KEYWORDS: Intestinal permeability; Glycation; Allergy; Metabolic syndrome; Glutamine; Curcumin.

INTRODUCTION

The intestinal wall represents a first-line, very efficient barrier for many potentially harmful alimentary or bacterial substances.[1] Increased intestinal permeability (IP) is a common problem found in several diseases that directly affect the gut, including common conditions such as irritable bowel disease (IBD) and more severe diseases such as Crohn's disease, celiac diseases[2,3] and other pathologies.[4] Therefore, it is conceivable that substances that normally do not or only slightly cross the intestinal wall can exert pathological effects under such disease circumstances.

Food allergies[5,6] and metabolic syndrome are common complaints in daily general practice, and the reported increases in the prevalence of these disorders may be associated with the abnormal passage of elements into the general circulation. The present article will show supporting evidence for this hypothesis and suggest that natural inhibitors of IP, such as glutamine, may be useful for these disorders. However, severe clinical conditions will not be addressed herein. A role for the diet in modulating IP will be discussed.[7] In view of the rising problem of modern food processing (solid aliments, beverages),[8] we have selected glycated proteins and lipids as particularly relevant and interesting examples to illustrate how diet modulates IP.

INTESTINAL BARRIER / INTESTINAL PERMEABILITY

Prevention of the entrance of toxic or infectious molecules, such as solutes, antigens and microorganisms, is ensured by the gastrointestinal lining. A key structure of the intercellular space is the tight junction, which plays a major role in regulating the paracellular passage of luminal elements.[9,10] Therefore, proper functioning and regulation of tight junctions is crucial. These junctions are under the influence of intestinal microflora, inflammation and even alimentary components, which can compromise tight junctions. Detailed information on the structures involved in tight junctions and their connections with the immediate

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anatomical environment can be found in dedicated reviews.[11,12]

Active debate has focused on the causal mechanisms of increased IP. This phenomenon may be directly due to local contact with luminal stimuli or may be secondary to increased transcellular transfer of antigens, thereby activating mast cells and disrupting tight junctions via inflammation.[11,13,14] Cytokines such as TNF-α and various interleukins play a prominent role in tight junction disruption[15,16]

Increased permeability (or "leaky gut") is typically observed in IBD,[2,17,18] but it is also seen in various pathologies that are initially indirectly related to gut disorders, including inflammatory response syndrome, allergies, asthma and even autism.[19] The autoimmune disorder type 1 diabetes may involve IP,[20,21] whereas type 2 diabetes does not seem to present this disturbance.[22] Infections or stress can also lead to perturbations of the intestinal barrier, meaning that initial structural defects of the barrier are not necessary to develop food allergies.[23] Conversely, the presence of IP is not uniform among patients, although the majority of IBD patients and subjects with pseudoallergic reactions in chronic urticaria present IP.[24] In patients with food intolerance, hyperpermeability was observed in approximately half of the studied population,[25] whereas other investigators have reported a very high prevalence in patients with either food allergies or hypersensitivity.[16] The reversibility of the defect is controversial, given that some data suggest that withdrawal of the food allergen for six months was not accompanied by IP improvements.[16]

Taken together, these data strongly support the hypothesis that in cases of elevated IP, the increased passage of substances that are normally largely or completely blocked by the intestinal barrier do gain systemic access. These substances may cause deleterious effects on health, producing allergies and metabolic and/or vascular changes.

FOOD PROCESSING AND NON-ENZYMATIC GLYCATION

Glycation, AGEs and ALEs

A normal diet contains relatively low levels of glycated proteins or lipids. Non-enzymatic glycation occurs in a series of conditions, the best known of which is elevated temperature. The combination of high temperatures in industrial food conservation, flavoring and daily home cooking with increased use of sugars has led researchers to investigate the content of advanced glycation end products (AGEs) and glycated lipids (ALEs) in modern food and to study their possible harmfulness. AGEs are the final product of a chain of reactions in which reducing sugars spontaneously react with aminopeptides, lipids and nucleic acids. This reaction initially creates so-called browning products (glycotoxins) due to the Maillard reaction. Amadori products are formed later in the reaction, and AGE is finally formed via recombination. The best-known AGEs are carboxymethyllysine (CML) and pentosidine, for which several measurement techniques have been developed based on their fluorescent nature. However, amino-containing lipids are also subjected to glycation and represent an important component of high-fat diets. Various chemical reactions during this process generate free radicals.[26] Once formed, AGEs induce inflammation,[27,28] which may further exacerbate IP. The formation of AGE/ALE is strongly accelerated by cooking in the moderate to high temperature range.

Pharmacokinetics

Normally, dietary AGEs cross the intestinal wall poorly;[29,30] AGE transport across the intestinal epithelium is low and occurs via simple diffusion.[31] After intravenous administration, AGEs are largely eliminated by hepatic sinusoidal Kupffer and endothelial cells.[32] However, elimination might be very different if IP is elevated and may be more threatening if renal function is also impaired, limiting urinary excretion of AGEs. Minimal data exist regarding the pharmacokinetics of AGEs, and data on absorption rate of glycated products are variable; pyrroline and pentosidine appear to be well absorbed, while peptide-bound Amadori products are not.[33] These varying findings may be due to the capacity of intestinal epithelial cells to degrade these various compounds. However, it should be noted that data exist only for some selected, measurable AGEs, while myriad different AGEs exist due to permanent recombination among AGEs. Consequently, the actual amount of AGEs absorbed may exceed the values obtained thus far.

Glycation in food

Comparison of different cooking methods has shown that identical substances can behave very differently. For example, strongly roasting typically increases allergenicity of peanuts.34 In addition, carboxymethyllysine content is significantly higher in infant formulas than in breast milk.[35-37] High-fat meals have the highest AGE content, more than meat and carbohydrate-rich meals. This also depends on the cooking method because broiling and frying generates more glycated compounds than roasting, and the least

amount of glycated compounds is generated by boiling.[38] Thus, the safest cooking method appears to be slow boiling at reasonable temperatures. Alpha-dicarbonyls (the most prone to form glycation), which are found naturally in green coffee, increase if beans are subjected to light or medium roasting, while dark roasted coffee contains fewer of these compounds.[39] Therefore, very high temperatures during food processing denaturate proteins that have lower glycation capacity. Consequently, the recognition of epitopes by IgE is diminished.[40,41] In parallel, protein digestibility is lower if the diet is rich in browning products.[42] Glycation of food allergens increases T-cell immunogenicity of food allergens.[43] Finally, postprandial leptin concentrations, which are lower in diabetics, improve if meals are heated with low temperatures.[44]

Recently, strong concerns were raised regarding increasing consumption of sweetened beverages. Researchers have begun to suspect a link between the high intake of reducing sugars and the incidence of metabolic dysregulation, such as metabolic syndrome, in younger populations. Sweetened fruit juices contain high levels of fructose, and levels are significantly greater than those found in whole, fresh fruits.[45] Fructose is linked to metabolic syndrome, hyperlipidemia and type 2 diabetes.[46] Methylglyoxal, a strong glycating agent, is also present in many beverages.[47] Tea, coffee, diet coke and soy sauce have a high AGE content. In diabetic patients, fructose absorption is increased by prevailing hyperglycemia. In addition, kidney function is often compromised in these patients, which suggests that dietary AGEs add to those synthesized endogenously by the high glucose levels.[30]

The impact of glycated products on health

Increased passage of glycated compounds into the systemic circulation is expected to induce at least two pathological situations: allergies and metabolic disorders.

Allergies

Although only minimal data exit on AGEs and allergies, the existing data are consistent with our hypothesis. The induction of IP by tacrolimus leads to more food allergies.[11,48] Exposure of intestinal CaCO2 cells to methylglyoxal or glyoxal, two potent glycating metabolites, in vitro is followed by increased IL-6 and IL-8 formation, which amplify the effects of TNF-α and IL-1β.[49] Some data suggest that AGEs may cause intestinal inflammation on their own.[50] IL-9 has been reported to play a particularly important role in allergy by mediating the mast cell response. Indeed, IL-9 deficient mice do not develop anaphylaxis, whereas IL-9 overexpression does produce anaphylaxis.[51] IL-17 has also been suggested to be important in food allergies.[52] These inflammation signs have been confirmed in vivo. When dietary AGEs from casein form a complex with serum albumin, the receptor for AGE (RAGE) is stimulated and induces inflammation.[27,53] RAGE is expressed in the intestinal epithelium and increases when interferon γ or TNF-α are high, such as in IBD.[54,55] Samples from IBD patients have confirmed that RAGE increases and that NF-B is activated.[56] As a sign of allergenicity, IBD subjects were shown to have elevated IgG levels response to some foods,[57] confirming the findings of various studies of gastrointestinal diseases in dogs.[58] When compared with raw food antigens, IgE antibodies were elevated four-fold against processed food antigens in 30% of humans.[59] The allergenicity of peanuts relates to their curing temperature (77 °C) and roasting.[60] Similar findings have been reported for soybean-based products.[61] Finally, AGEs can also modify the gut microbiota.[62] Thus, although we could not find direct data on food allergy prevalence among patients with increased IP, this set of surrogate measurements strongly supports an association between food allergies and IP.[63]

Metabolic disorders

The recent recognition that dietary AGEs are absorbed and the fact that AGE consumption is constantly increasing in the westernized diet have prompted investigations on possible causal relationships between AGEs and observed metabolic disturbances. A first-line candidate for a link in the causal relationship is fructose, a relatively strong glycating sugar widely used in sweetened beverages and corn syrup.[64] For example fructose consumption correlates with worldwide obesity and diabetes prevalence. Chronic intake of sweetened beverages increases triglycerides and ApoB concentrations in obese patients.[65,66] Recently, a Brazilian study revealed that high intake of dietary fructose was associated with glucose intolerance.[45] Approximately one-third of IBD patients present with fructose intolerance.[67] In these subjects at least, fructose may have harmful effects. Fructose is lipogenic and can provoke non-alcoholic steatotic hepatitis (NASH).[68] Whether normal levels of dietary fructose intake increase glycation in healthy subjects remains a matter of debate.[69-71] One reason for the debate is that while fructose is more reactive than glucose in AGE formation, blood concentrations of fructose are low.[72] When rats are fed a high-fructose diet, the AGE pentosidine accumulates in the aorta and skin.[73] Similarly, comparison of different sugars in rats showed that glycation and oxidative stress occurred preferentially in fructose-fed animals.[74] While it is not known whether humans handle dietary fructose like

rodents, it should be stressed that chronic fructose-feeding, whether in pellets or in the drinking water, is one of the best experimental models to simulate metabolic syndrome and the evolution toward human diabetes. Recent studies have suggested that the diabetogenic effect of fructose occurs via increases in uric acid.[46,75] Therefore, fructose consumption should be kept to a minimum.[76-78]

A chronic diet including 1% methylglyoxal induces insulin resistance and salt-sensitivity in Sprague-Dawley rats.[79] A high-fat diet has also been shown to be a good model to simulate human metabolic syndrome. Accordingly, rodents chronically kept on high-fat diets exhibit insulin resistance, dyslipidemia and finally diabetes in a majority of animals within six months.[80]

As described above, high-fat diets contain high levels of AGEs and ALEs. Thus, high AGE and ALE levels may represent risk factors for human health by favoring inflammation in various organs, at least if subjects have compromised organ function.[81] The processing of food to induce high AGE levels leads to adipocyte dysfunction, as shown by reduced leptin and adiponectin production as well as the increased oxidative stress.[82] The autoimmune origin of type 1 diabetes has been linked to increased IP, and a prominent involvement of gliadin in IP activation, which can activate pancreatic T cells, has been proposed..[20] Gliadin stimulates zonulin signaling, leading to intestinal hyperpermeability.[83] Very interestingly, type 2 diabetic patients were shown to have increased zonulin.[84] Furthermore, in diabetic db/db mice, restricted intake of oral AGEs improved insulin sensitivity.[85] Several mechanisms have been proposed to explain how AGEs lead to insulin resistance via the AGE receptor,[86,87] but direct structural modifications of insulin itself by methylglyoxal have also been shown.[88] The harmful association between nutrition, hyperglycemia and impaired renal function may relate to AGE intake in humans.[89] Nevertheless, the causal implication of food-derived AGEs on these three outcomes is still debated and worthy of further investigation.[90,91] Two clinical studies are presently being conducted to more closely evaluate the impact of AGEs on human health.[92,93]

A high-fat diet increases visceral AGEs and promotes DNA fragmentation and apoptosis in the liver.[94] Obese mice have NASH and increased IP, rendering hepatic stellate cells sensitive to bacterial endotoxins.[95] Moreover, chronic liver diseases are linked to increased IP,[96] which is important when considering that most prediabetic and diabetic patients have NASH.

Other pathologies

Lifespan was shown to be extended in mice fed low-AGE diets, suggesting that AGEs are involved in aging.[97,98] In addition, atopic dermatitis has been proposed to involve dietary antigens; however, this proposal remains a matter of debate.[12] Furthermore, patients with ankylosing spondylitis and their relatives present with increased permeability in the small intestine,[99] and Campylobacter infection increases IP, which can last up to one year postinfection.[100]

Cardiovascular disturbances

In certain rodent strains, fructose can lead to hypertension. For example, vascular reactivity in fructose-fed animals showed a 35% reduction in flow-mediated dilatation,[82] and adhesion molecules were also increased,[101] reflecting endothelial dysfunction. In diabetic patients, high AGE-containing meals are more harmful to microvascular function and oxidative stress than low-AGE food.[102]

TREATMENTS

As described above, strong support suggests that higher prevalence and severity of various diseases can be expected in the presence of intestinal hyperpermeability. Most of these diseases are chronic and can be treated by simple nutraceutical approaches. Consequently, improving IP may be a simple an inexpensive way to prevent aggravation of chronic diseases.

Glutamine

Glutamine is presently the best known compound for reducing IP, and nutritional depletion is known to result in increased IP.[103-106] Major abnormalities in IP have been demonstrated in glutamine-deprived rat pups.[107] Furthermore, glutamine has been shown to maintain transepithelial resistance and to reduce permeability in intestinal cell culture monolayers.[108] In addition, glutamine supplementation has been shown to increase intestinal barrier function in malnourished children.[109] However, glutamine has no effect if administered parenterally to depleted patients.[110] Glutamine is the preferential substrate for enterocytes, and it works in concert with other amino acids, such as leucine and arginine, to maintain integrity and function.[111] Several studies have demonstrated the beneficial effects of glutamine on IP. For example, improvements in the intestinal barrier have been shown in experimental biliary obstruction,[112] after ischemia/reperfusion[113] and even in severe clinical situations, such as in critically ill patients, in whom glutamine lowered the frequency of infections[114] following abdominal surgery.[115] Furthermore, in IBD treatment, the use glutamine alone or in combination with

other amino acids is considered promising.[116] In low birth weight children, allergies were improved by glutamine treatment during the first year of life.[117] These non-nutritive effects of glutamine have recently been reviewed,[118] and these effects have been ascribed to the antioxidant properties of glutamine and the enhanced expression of heat shock proteins.[119]

Curcumin

Curcumin (turmeric) has remarkable properties in inflammation and oxidative stress[120,121] and is a potent immunomodulator.[122] It is able to reduce acrylamide-induced injury in HepG2 cells.[123] In addition, it partly inhibits the fibrogenic evolution and oxidative stress in the steatotic mouse liver in vivo.[124] Curcumin has also been shown to be efficacious in experimental colitis[125] as well as in colonic inflammation in multidrug-resistant mice, which exhibit IBD.[126] Thus, curcumin might be a good candidate to treat IBD,[127] but it presents some theoretical limits. Indeed, like most antioxidants, curcumin should be used at moderate doses because at high doses it can enhance oxidative stress.[128] Moreover, curcumin is rapidly cleared and conjugated, which may limit its therapeutic effectiveness as a single agent.[129]

Although the precise mechanisms of action of both compounds (in particular glutamine) must be further elucidated, an association between glutamine and curcumin is interesting in view of their complementary mechanistic properties, which correspond well to the pathological disturbances characterizing intestinal epithelial cell injury. We believe that testing the association between the two compounds would be clinically worthwhile.

Other treatments

Pre- and probiotics are also of potential interest. In obese and diabetic mice, which exhibit increased IP, prebiotic carbohydrates lowered IP and hepatic expression of markers of inflammation and oxidative stress.[130] In humans, prebiotics reduced gut permeability in atopic dermatitis.[131] In addition, probiotic carbohydrates lowered IP and inflammation in metabolic diseases.[132,133] A mixture of streptococcus thermophilus and lactobacillus acidophilus protected the intestinal barrier in experimental colitis.[134] Leaky gut was also improved by the probiotic Escherichia coli Nissle 1917.[135] In addition, various substances have been tested and have been reported to have protective effects on IP; however, qualified studies on these substances are lacking.[136-138] Overall, approaches using pre- and probiotics still need confirmatory investigations.[139-141]

CONCLUSION

Intestinal hyperpermeability is found in many diseases, from specific mild or severe gastrointestinal diseases to various pathologies linked to metabolic disorders. The abnormal transfer of pathogens from the intestinal lumen into the systemic circulation leads to disturbances in various organs, including the liver where it seems to be closely linked to non-alcoholic steatotic hepatitis. Allergies and vascular problems also appear to involve elevated IP. We have attempted to illustrate how alimentary compounds induced via modern cooking, food conservation and food processing methods may be associated with these pathologies when IP is increased. These associations are certainly largely unrecognized and not necessarily easy to identify. The aim of this overview was to increase scientist awareness of this simple idea and draw attention to what we believe is a very common clinical situation. Although still at the conceptual level, we feel that much supporting data can be found through the literature to suggest that early use of natural compounds, such as glutamine or curcumin (or a combination of both), and possible probiotics in the near future might represent a simple method to prevent the appearance or aggravation of many chronic pathologies.

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