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REVIEW

The intestinal permeability syndrome, celiac disease, gluten sensitivity, autistic spectrum, mycotoxins and immunological tolerance

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Abstract The onset of several human diseases takes place in an inefficient intestine. We probably should re-evaluate the relationship between food and health. Three million Italians and twenty million Americans suffer from the gluten sensitivity syndrome, similar yet different from celiac disease. Different pathological status arise as a consequence of sensitivity to gluten, depending on the genetic polymorphism of the subjects and the environment in which they live. If we gain more knowledge on interactions between food, eating habits, genomics and the environment, this could mean better prevention and/or treatment. The era of epigenetics has begun, while the dogma of genetic determinism seems to be fading.

Keywords Mycotoxins · Immunological tolerance · Intestinal permeability syndrome · Celiac disease · Gluten sensitivity · Autistic spectrum

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Intestinal permeability

Several investigations indicate that the gastric-intestinal barrier is highly dependant on the genome of intestinal bacteria [1–3]. An intestine with questionable bacterial flora compromises the production of digestive enzymes affecting normal biochemical conditions, (pH levels, vitamins, peptides and bacteria) and generates secondary minimal submucosal inflammation [4–6]; it can also alter some enzymatic patterns present on cell membranes, in particular on the microvillus (one notable case is that of lactase) [1, 7].

Under normal conditions, the microvillus sustain physiological digestion and absorption of micronutrients, while in abnormal conditions they could determine the passage of macromolecules beyond the gastric-intestinal barrier (GIB) [8], which, due to their size, could be identified as non-self and, resulting immunogen, could trigger an immunological response [9, 10].

The gastric-intestinal epithelium is normally a selectively permeable barrier and its function is determined by the formation of protein–protein complexes, desmosome junctions, hemidesmosome junctions, gap-junctions, adherens junctions and tight junctions. The latter, mechanically connect adjacent cells sealing intracellular space. Over the last decade, more attention is being paid to the tight junctions, because their alteration could cause a break-down in the barrier function which helps to promote immunological reactions (autoimmune and inflammatory diseases) [11, 12].

Experimental evidence [13, 14] suggests that dysfunction of tight junctions is a contributing cause, and perhaps the main cause for the onset of systemic immunological inflammatory diseases, inflammatory bowel disease (IBD), food allergies and celiac disease [15]. It seems these may

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be contributing factors to the development of Autism [16–22].

Overall, the results of these studies show or at least seem to suggest that diseases associated with the leaky gut syndrome may disappear and/or stop if the patient's intestinal barrier function is restored. The evidence in support of this is still incomplete, but solid enough to encourage researchers to continue on this path [2].

The tight junctions are the primary target of external agents, which act as chemical and/or biological pollutants [13, 23]. They can interact with the protein matrix of the joints, altering the conformation and thus increase permeability for external agents [24].

Our observations have been identified via the unaware ingestion of biological contaminants (mycotoxins) and subsequent sporulation dysbiosis of Candida [25], factors that could determine leaky gut syndrome. This could establish a new balance of the microbiota [26–29] which can often result in relevant clinical signs or symptoms [15, 28].

In any case, the timing of the onset of typical symptoms of the syndrome should be checked, also in relation to age. It may be necessary to understand the reason why in some subjects there is no outbreak and if it is a temporary or permanent situation. A study of this kind may reveal other mechanisms, probably of the immune system, which are still unknown.

Immunological tolerance: celiac disease, gluten sensitivity

The most particular feature of celiac disease is undoubtedly the environmental factor that causes it: gliadin [30–37]. It is an immunogenic peptide, resistant to pancreatic and gastric enzymatic digestion which only because of modifications to the tight junctions, are able to reach the lamina propria (part of the intestinal mucosa), where the immune response takes place [38]. In other words, unless the door is opened, you cannot pass.

However, it is precisely here, at the level of the lamina propria where transglutaminase tissue type II (tTG) catalyzes covalent bonds between glutamine and lysine [39]. The deamminated peptides thus create epitopes (part of the antigen that binds with the specific antibody) with an increased immunostimulatory potential [40].

With this modification there is an increased affinity of the antigens, presented by the APC (antigen-presenting cell) to the macrophages, to the B-lymphocytes and to the T CD4+ (lymphocytes helper), with the HLA system II (human leukocyte antigen II) and then with the two genes or protein molecules DQ2 and DQ8 produced by them [41–43]. Lesions of the intestinal mucosa (villous atrophy and crypt hyperplasia) detectable with biopsy, are the result of the dynamics of this immunological process and adaptable over time [44]. Although we are aware of the genetic component in celiac disease with increased risk of disease in first degree relatives [45], (the concordance in monozygotic twins is over 75 % and concordance in dizygotic twins is of 13 %), there should always be a "primum movens", which may well be the opening of tight junctions. Gluten sensitivity, on the other hand, is not a mild form of celiac disease (CD), but a disease itself [46]. While it is different from the molecular and immune point of view, the cause may be the same: the opening of the tight junctions. The fact that 1 % of people worldwide are suffering from gluten sensitivity [47] could explain the interest in this morbid condition and its possible evolution to the typical form. Gluten sensitivity (GS) does not present alterations of the intestinal permeability; [48] it probably only manifests the submucosal inflammation which, as we know, is significantly greater in celiac disease [49]. "In celiac disease an autoimmune mechanism is activated, conditioned by an adaptive response of the immune system, but in GS, there is a genetic mechanism that involves the innate immune system, without involvement of the intestinal barrier function, where there are signs of infection but not damage, as occurs in celiac disease" [23].

To date, there are no laboratory or histological tests able to confirm this type of "reactivity"; as a result, it is a diagnosis which is reached by exclusion. The diagnosis will be followed by nutritional changes with elimination of gluten and an open challenge (a controlled re-introduction of food containing gluten) to assess if there is a real improvement of symptoms based on reduction or elimination of gluten from the diet and if this protein food is reintroduced, the disorders reappear.

We can establish that the precipitating factor in both CD and GS is gluten, but another external or environmental factor should be considered: mycotoxins. Therefore, it could be said that food becomes the common denominator of the damage, not only for its content of macronutrients, quality and quantity, but also because of the different mycotoxins that may synergistically contribute to the leaky gut syndrome [21, 50]. Among the major mycotoxins probably involved that favour the syndrome (aflatoxins, ochratoxins, etc.), our attention has focused on deoxynivalenol (DON). Due to ease of contamination of most common foods such as pasta and bread, mycotoxins including DON, the most studied, are particularly fond of tight junctions [8]. This could be related to an innumerable quantity of clinical manifestations that occur for no apparent reason. Future research should be intensified on a larger number of mycotoxins and their mutual interactions.

Over the last hundred years man has tried to favour genetic rearrangements, producing interspecific hybrids in the genus *Triticum* (wheat) and intergeneric between

Triticum and *Secale* (Triticale), to improve yields per hectare [51]. To our knowledge, and based on a strictly scientific basis, nobody has ever tested to see if these genetic changes have favoured an immunological response, and therefore increased or not the conditions that lead to celiac disease, GS, autism and possibly other diseases in the last 30 years. The Toulouse INRA [8] has studied the molecular mechanisms and the immune response to grain, flour and pasta free of mycotoxins with particular reference to DON. Perhaps, there is already an answer in the results of these studies, but deeper investigations are necessary or further testing before coming to a definitive solution on this issue—namely whether the genetic changes induced by artificial mutations and crosses have some relationship to celiac disease and autism [16, 17, 52, 53]. It is also necessary to consider another factor which could be relevant: lectins. The genetic difference between types of wheat is also due to proteins called lectins, which are not only in saprophytes and pathogens, but also in food and on the membrane of blood elements, in particular red blood cells [54]. When we consume food containing lectins incompatible to our recognition code, we activate a minimal immune response (minimal Flogosis), so even lectins could trigger damage to the walls of the digestive system. If the same food also contains mycotoxins (in meaningful biological quantities), such as DON, they may support the hypothesis of a response with clinically relevant symptoms. In other words, lectins would be giving the green light to mycotoxins (macromolecules). Could lectins be opening the door? For these reasons and to evaluate the actual dependence on gluten of the clinical abnormalities highlighted in patients with gluten sensitivity (GS), a group of researchers who are part of the "CAMPO Consortium" and the "Dino Leone Foundation" from Bari, have started a research to study the relationship between nature, food composition, mycotoxins and the immune system.

Deoxynivalenol (DON or vomitoxin)

The deoxynivalenol (DON) is a mycotoxin, one of the metabolites of some fungi (molds) belonging to the genus *Fusarium* (*F. graminearum* and *F. culmorum*, etc.). These can be considered "natural and involuntary toxic factors", carcinogenic, teratogenic and mutagenic [55]. More toxins may originate from the same fungi, as in the case of *Candida* (*Candida albicans*) and there may be synergies between different toxins, as in the case of ochratoxin A (OTA) and citrinin.

On a global scale, the DON mycotoxin is by far the most frequent and the most feared and therefore the most studied. It could particularly contaminate cereals and their derivatives (flour, bread, etc.). Considering its extreme stability (heat stable) during the different technological treatments, and the almost total absence of decontamination processes, it could easily be found in the finished food. It may be necessary to characterize the toxic effects of DON, in particular on the entire intestine, including the stomach, the first organ to be in contact with food. This mycotoxin could reduce the barrier function of the intestine (reduction of the electrical resistance of the epithelium, increased cellular permeability to molecules, and increased passage of bacteria) [56]. The alteration of the barrier function GIB could be associated with a reduction of protein function (claudins) [57] in a particular region of the intestinal tissue, the so-called tight junctions. These act as a "hinge" between the intestinal cells. This was observed both in cell culture and in the intestines of piglets that had ingested contaminated food.

DON could reduce the function of the intestinal barrier, probably causing an increase of bacteria passage through the intestine. The intestinal permeability would thus be altered. This could have important consequences in terms of susceptibility to infections (*Salmonella*, *Escherichia*, etc.) [58]. The transit of pollutants such as heavy metals and pesticides may then increase the harmful effects and local and systemic immunological responses may occur. This may affect the prognosis of diseases such as gluten sensibility and autism. The induced damage could also offer indirect assessments of great interest, since the mucosal disorders could slightly change the cellular biochemistry function. There may be a lack of Vit B 12 for the reasons set out above, and then a decrease of desaturase, and this would explain the alteration of the membrane, low in polyunsaturated and rich in saturated (phosphoglycerides). At the gastric level, the absorption of vitamin B12 may be penalized, which needs to be synthesized through the intestinal intrinsic factor (IF) (or gastric or castle). A B12 deficiency could prevent the physiological conversion of homocysteine to methionine. According to an individual's predisposition to this, clinical signs may then appear. DON can easily be found in school cafeterias, kindergartens and primary schools, especially in bread and to a limited extent in pasta [7]. The industry of these products should be obliged to work with the wheat paying more attention to contamination in the field and implement specific fermentation processes reducing the amount of mycotoxins.

Autism: an emergency?

After Reichelt's work [59], the number of authors who highlight the presence of high levels of peptides "opioids" (casomorphine and glutomorphine) in the urine of children with autism has increased [60]. This evidence may suggest

that children with autism, during the digestive process, due to an altered digestion of these proteins caused by mechanisms which are not yet clear (but still imply the involvement of tight junctions), absorb abnormal peptides that influence the mechanism of neurotransimssion [59], as they manage to overtake the blood–brain barrier. These molecules, due to their affinity to the μ receptors, may contribute to the cause of the behaviour of these patients [19]. For this reason, often they are put on a diet free of such foods [60]. A period of abstinence from gluten and casein, which varies depending on the case, could lower the levels of opioid peptides [61]. Results seem very encouraging, especially when applied before pre-school age, in the early years of life when potential development and neural plasticity are still very active. These considerations could become mandatory in all pregnant women with a family risk factor, especially if we take into consideration some studies that indicate high levels of mycotoxins in the umbilical cord, higher than in plasma. Dysbiosis follows the alteration of tight junctions [3, 25]. It is known that after restoration of balance (eubiosis [25]) intestinal permeability decreases, simultaneously improving the general health of children [12].

The positive side of the natural diet without gluten and casein is expressed by the significant improvement achieved by the children who follow this diet: increased attention, improved interactive capabilities, regression of hyperactivity, lower violent behaviour, increased resistance to infection and better quality sleep [19].

Conclusions

The results of extensive research may encourage further study on the effects of food contaminated by mycotoxins, both in human and animal diets, thus avoiding pollution of the entire food chain. This would be the road to reducing the problem of intestinal permeability, breeding ground for different pathologies. Currently, one of the goals of researchers is to understand the delicate immunological balance probably related to the consumption of foods rich in "heavy" gluten, and evaluate consumption in relation to the rapid spread of diseases related to gluten. The grains of industrial agriculture, which for the most part are hyper-fertilized, often grown in environments which favour contamination by fungi with consequent development of mycotoxins. These grains contain a higher proportion of gluten, up to 12 % more compared to non-hyper fertilized ones and seem to make life difficult not only for border-line patients of celiac disease, but for all subjects with correlated immunological manifestations including the "metabolic syndrome". It therefore seems that increasing sensitivity to different diseases is determined by the increased use of modern grains, with more gluten at the expense of older grains with less gluten, and with which man has evolved. For some this is still a hypothesis, for others a certainty. The task of the research, carried out by multidisciplinary working groups, should be to eliminate every shadow of doubt as far as possible.

Conflict of interest None.

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