# Health related effects of wheat varieties

Agrologica. Internal report

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## The human diet

The neolithic revolution resulted in a dramatic change in human nutrition. The Mesolithic diet was rich in fibre, antioxidants, essential oils and amino acids, but short in energy. The introduction of cereals and other crops drastically increased energy intake on the expense of other nutrients, resulting in rapid increase in birth rate and human population, but at the same time changed the nutritional status of mankind. When the grain based diets replaced the traditional diets of the Mesolithic hunter-gatherers, lifespan and stature decreased, while infant mortality, infectious diseases, bone mineral disorders, and the frequency of dental caries increased (Cohen, 1987). The height of people decreased due to the changed diet as a sign of general malnutrition, and despite improved nutrition and increasing height over the past century, we are still 3 cm shorter than our pre-agriculture ancestors (Murphy, 2007).

The major health issues in western societies are cancer and cardio-vascular diseases coursing the death of over 60% of the population (Heather et al 2011), but also less lethal diseases such as allergy, diabetes, chronic inflammation and obesity are involved in the lifestyle syndrome, most of which are more or less interrelated with each other and with cancer and cardio-vascular diseases (Kooene et al 2016). In 2012, the prevalence of type 2 diabetes in Denmark was 320.000 subjects and another 300.000 suffered from pre-type 2 diabetes. Alarmingly, incidence is estimated to reach 430.000 in 2030 (www.diabetes.dk). Many different factors contribute to our life style diseases, including smoking and physical inactivity being the main risk factors, but even for physical active non smokers, the mortality risk is 25% higher for people with unhealthy diet, and significantly higher than that when combined with other risk factors (Haveman-Nies et al. 2002).

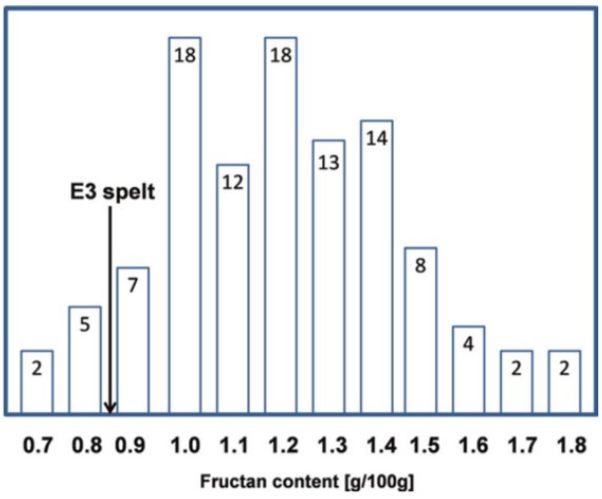
In The UK, wheat and other cereals accounts for 45% of the carbohydrates intake and 23% of the proteins (Shewry and Hey 2015). Also in Scandinavia and other Western European countries, wheat is by far the most consumed crop in the modern diet. Therefore, if the nutritional status of wheat can be improved, this could be one of the most significant factors for human health, well-being and survival.

## Wheat

Wheat contains both soluble and insoluble dietary fibres, but less so compared with rye and barley. Lack of dietary fibres is one of the risk factors in Western diet. Dietary fibres, and in particular soluble dietary fibers increase viscosity of fluids in the colon and improve nutrient uptake such as calcium (Lopez et al. 2000; Scholz-Ahrens et al. 2001; Abrams et al. 2007a,b). Studies have shown several positive effects of whole grain wheat consumption on several life style diseases, e.g. type 2 diabetes, cardio-vascular disease and cancer (Björck et al 2012, Sereni et al 2017).

In wholemeal wheat flour, the total dietary fibres ranges from 10-15%, but most wheat is consumed as white sifted flour, which contains much less. Only 6% of the Danish population consume the recommended ratio of wholemeal grain products. The more significant fibres are therefore those contained in the endosperm ranging only from 1.9-6.3% in standard varieties (Shewry and Hey 2015). The huge variation in dietary fibres in white flour could therefore be a tool for increased intake of dietary fibres.

While dietary fibres are in general beneficial to our diet, some patients suffers from irritable bowel syndrome (IBS) or inflammatory bowel diseases such as Crohn's disease or ulcerative colitis due to fructose malabsorption or dysfunctional gut microbiome. IBS is a very prevalent disease that affects an estimated 11.5% of Europeans (Hungin et al 2003). For such patients, rather than consuming high fibre wheat products, products with low content of fructans, lactose and raffinose can decrease symptoms or cure the syndromes by reducing fermentation in the colon (Gibson and Shepherd 2010; Muir and Gibson 2013). In wheat, these fructans are considered as dietary fibers and serve the purpose of increasing tolerance to cold and drought in the wheat plants (Calderon and Pontis 1985; Hendry 1993).



Variation of fructan levels in 105 spelt cultivars grown in Hungary at the same location.

The unique health benefits of whole grain products are not only due to dietary fibres, but also to phytochemicals present in the brand and aleurone layer, including phenolic acids, flavones, flavonols, and anthocyanins contributing to the total antioxidant potential.

Purple wheat in particular has higher content of both phenolic compounds and anthocyanins compared with both normal red wheat and white wheat ranging from 0.01mg/g total flavonoid in normal red wheat and white wheat, up to 1.02mg/g in the best purple wheat. For anthocyanin the content ranges from 0.01 in red wheat and white wheat, to 0.23mg/g in purple wheat (Qin et al 2010).

Carotenoids, the most widespread pigments in nature, are liposoluble antioxidants produced by plants, algae, fungi, and some bacteria. In plants, carotenoids contribute to the photosynthetic process by acting as light collectors and photoprotectors (Britton et al 1995). The general health benefits of different carotenoids are well known and accepted including protection against a range of chronic diseases, such as cardiovascular diseases and cancer (Mayne 1996, Cooper 2004, Britton 2009). In particular, lutein plays an important roles in the prevention of eye diseases such as age related macular degeneration (AMD), cataracts, and retinitis pigmentosa (Landrum and Bone 2001).

Wheat species differ in concentration of lutein. Einkorn varieties has the highest total amounts of lutein (4.5-7.8 µg/g DM), followed by durum (2.0-4.6 µg/g), spelt (0.9-2.0 µg/g), emmer (0.8-1.9 µg/g), and bread wheat (0.7-2.0 µg/g). Due to the observed highly significant genetic variance and high heritability, lutein contents of wheat genotypes may be increased by future plant breeding. (Ziegler er al 2015).

## Expansin

A divergent group of β-expansin genes are expressed at high levels in the pollen of grasses but not of other plant groups. These pollen proteins were identified by immunologists in the mid-1980s as the main causative agents of hay fever and seasonal asthma induced by grass pollen (Cosgrove 2000). More than 95% of patients allergic to grass pollen possess IgE antibodies to expansin (Grobe et al 1999).

Expansin is also expressed in seed, and one spelt variety, E3, have been identified with a mutation in the gene coding for expansin.

## Wheat allergy and celiac disease

Autoimmune diseases is one of the lifestyle diseases developing rapidly on Westerns societies in epidemic scale. In USA these diseases affects today up to 8% of the population. Wheat allergy and the autoimmune celiac disease, which are mediated by adaptive immune systems, are the most known diseases related to gluten. Under both these conditions, gluten reaction occurs via T-cell activation at the gastrointestinal mucosa level. Cross-linking between immunoglobulin (Ig)E and gluten epitopes is responsible for **wheat allergy**, and it triggers the release of chemical mediators (e.g., histamine) from basophils and mast cells. **Celiac disease** on the other hand is an autoimmune disorder, which mainly involves the response of serum anti-tissue trans-glutaminase and anti-endomysial antibodies. Other cases of reaction to gluten are commonly described as **Non Celiac Gluten Sensitivity (NCGS)** or Non Gluten Wheat Sensitivity (NGWS), and they do not involve allergic or autoimmune mechanisms. Intestinal (e.g., diarrhea, abdominal discomfort orpain, bloating) or extra-intestinal (headache, lethargy, attention-deficit/hyperactivity disorder, ataxia or recurrent oral ulceration), symptoms are often manifested during NCGS (Di Sabatino and Corazza, 2012).

The prevalence of wheat IgE sensitization in European countries is 2.9% (Zuidmeer et al., 2008; Siles and Hsieh 2013).

The prevalence and the risk of death in undiagnosed celiac disease have increased dramatically during the last 50 years in the United States (Rubio-Tapia et al. 2009). Lohi et al. (2007) described a doubling of the prevalence of celiac disease in Finland in the last two decades, which definitely could not be ascribed to improved detection only. Also Rubio-Tapia et al 2009 documented up to 4 times increase in celiac disease incidence over the last 50 years . Several authors have questioned whether the last 60 years of breeding produced wheat varieties with more reactivity (Davis 2011; Junker et al. 2012), while others consider modern wheat processing to be implicated in epidemiological changes (Di Cagno et al. 2010).

Wheat proteins can be classified into albumins, globulins, gliadins, and glutenins, according to their structural properties and solubility. The protein in commercial wheat varieties contains approximately 10%–20% albumins/globulins and 80%–90% gluten, a complex mixture of gliadins and glutenins that are partly resistant to gastrointestinal enzymatic proteolysis that forms into gluten when knitted with water. Whereas gluten are structural protein mainly found in the endosperm of the seed important for the baking quality of the dough, albumins and globulins are mainly found in the aleuronlayer between the brand and endosperm and constitute up to 14 families of enzymes and other proteins involved in the germination and dormancy of the seed, and protection of the seed against pests and pathogens.

The unique food-industrial properties of gluten are in part related to a very high proline content that renders gluten relatively resistant to enzymatic degradation in the gastrointestinal tract. (Marti et al 2005; Piper et al 2004; Shan et al 2002). Hence, many of the immuno-genic gluten peptides are likely to survive for extended periods in the intestine, increasing the probability of triggering a T-cell response. This resistance to digestion is supported by anti-nutrients in wheat including ATI and phytin (see below).

The classical paradigm of autoimmune and inflammatory pathogenesis involves specific genetic makeup and exposure to environmental triggers. There are at least 50 toxic epitopes in gluten peptides exerting cytotoxic, immunomodulatory, and gut permeating activities (Nikulina et al 2004). A strategy to exclude all 50 toxic epitodes from wheat by plant breeding is hardly realistic at least in the short term. However, preventing the epitodes from entering the blood stream by improved integrity of the intestine might prevent a significant portion of problems. AT-1001 is a protein inhibiting release of zonulin, and it has been shown that AT-1001 can prevent celiac symptoms by patients exposed to gluten (Fasano 2013). When gluten containing the celiac triggering α-gliadin p31-43 are fed to CD sensitive mice with absence of ATI, the response to gluten is insignificant (Zevallos et at 2017).

Gliadin hydrolysis at pH 4.25 (Bottari and others1996) and the optimal pH for yeast enzymatic activity in degrading wheat fructose was 4.5 to 5 (Nilsson et al. 1987). However, an acetic environment is not only factor controlling digestion, as the chemical acidification has proven less effective than microbial or endo-protease degradation. In celiac patients, chemically acidified bread triggered more intestinal permeability than bread fermented with diverse microbial cultures (Di Cagno et al. 2004).

The level of flour refinement on celiac immono-reactivity responses has not been directly assessed (Kucek et al 2015). Allergenic peptides are found throughout the kernel. Many of the celiac-reactive α-gliadins are located in the subaleurone layer of the wheat kernel, which can be partially removed by roller-milling. However, the γ-gliadins and the HMW glutenins, which are reactive in a lower number of celiac patients, are concentrated in the endosperm, and will therefore appear in high concentrations also in white flour. Omega-gliadins, which are found throughout the grain, will likely not change with the level of flour refinement (Tosi et al 2011). Hence, there seems to be little evidence that white flour in general have more allergens triggering celiac disease as such. However, most endo-peptidase activity was found in the bran rather than the endosperm (Hartmann et al. 2006; Schwalb et al. 2012). Because the bran is removed in the process of making white flour, subsequent products has fewer enzymes available for prolamin degradation (Kucek et al 2015). The higher fibre content in whole wheat flour will increase to time of food passing the stomach and intestine and give the enzymes time to degrade the immuno-reactive peptides. There may in these ways be positive effects of whole grain products compared to white flour, even though the initial amount of immuno-reactive peptides are similar.

Gluten peptides recognized by T cells in the context of DQ2 and DQ8 have been identified in gliadins, glutenins, hordeins, and secalins. Tye-Din et al. (2010b) reported that α- and ω-gliadins appear to harbor most T-cell-recognized epitopes, while fewer T-cell epitopes are found in γ-gliadins and glutenins. A digestion-resistant α-gliadin peptide, LQLQPFPQPQLPYPQPQLPYPQPQLPYPQPQPF, referred to as 33-mer, is one of the highly immunogenic peptides that is often used as a marker for celiac immuno-reactivity (Arentz-Hansen et al. 2000). In addition to gluten, some wheat ATIs are also considered causative agents that mediate intestinal inflammation by binding to toll-like receptor 4 (Junker et al. 2012).

Species that lack the D-genome of wheat, such as einkorn, emmer, and durum, appear to exhibit average lower reactivity than common wheat, as several highly immunogenic α-gliadins are encoded by the D genome of wheat (Molberg et al 2005; Spaenij-Dekking et al 2005; van Herpen et al 2006).

In a screening of blood samples from patients suffering from wheat allergy, 63% were more allergic to wheat compared to spelt, whereas 30% were more allergic to spelt than to wheat (Vu et al 2015).

Each wheat plant contains to several hundred copies of gliadin and glutenin genes, most of which are copies of α-gliadins and just a few are High Molecular Glutenines, but it is unknown whether all these genes encode proteins that are equally harmful for patients (Spaenij-Dekking et al 2005).

Strikingly, although all α-gliadins contained 1 or more T-cell–stimulatory sequences, the large majority of the LMW-glutenin and one third of the α-gliadin proteins did not contain the T-cell–stimulatory epitopes. Also, some of the HMW-glutenin proteins contains no or just a few T-cell–stimulatory sequences. This indicates that although some gluten proteins lack T-cell–stimulatory sequences, others may contain up to 6. Thus, considerable variability in the toxicity of individual gluten proteins do exist (Spaenij-Dekking et al 2005).

Several studies have suggested that the α-gliadins encode the immunodominant T-cell response inducing gluten peptides, although the γ-gliadins and glutenins have received much less attention.

However, one database searches, indicate that the γ-gliadins appear to contain T-cell–stimulatory sequences most frequently (Spaenij-Dekking et al 2005).

Two hexaploid varieties Weissahr Rotkorn Binkel (CGN-04210) and Sappo (CGN-12393) appear to contain low levels of 10 known peptides encoding for immuno-dominant T-cell, including the γ-gliadin peptides and lower levels ad Minaret (Spaenij-Dekking et al 2005).

Several highly immunogenic α-gliadins are encoded by the D-genome of wheat (Molberg et al. 2005; Spaenij-Dekking et al. 2005; van Herpen et al. 2006). Consequently, species that lack the D-genome of wheat, such as einkorn, emmer, and durum, appear to exhibit average lower reactivity than hexaploid wheat, and common wheat does not seem to differ from spelt is respect to celiac disease (van den Broeck et al 2010b).

Molberg et al. (2005) found substantially differences in amounts of celiac disease epitopes among einkorn varieties. The einkorn cultivar “Monlis” gave no difference in gastrointestinal complaints after 28 d compared with gluten-free rice (Zanini et al 2009).

Bread wheat has more than dobble the amount of immunoreactive gliadin (50.4 and 65.4 mg/g) than durum wheat (20 and 25.6mg/g) (Dodig 2009). Emmer and durum, which have the A and B genomes of wheat, thus generally appear to be less immunoreactive than common wheat, but more immunoreactive than einkorn. Gliadin derived from 2 durum varieties were less cytotoxic than those from a common wheat, when exposed in vitro to biopsies of children with celiac disease. Five times the concentration of durum was necessary to match the intestinal villi damage caused by the common wheat (Auricchio et al. 1982), but differences occur amongst tetraploid wheats, and some varieties do not differ from hexaploid wheat in respect of T-cell proliferation and release of IFN-γ compared with bread wheat (Vincentini et al. 2009). Despite lower reactivity overall, einkorn, emmer, and durum still produced reactions in 25% to 38% of tested patients’ T cells (Molberg et al 2005). A negative side effect of low immuno reactivity may be that allergenic emmer lines lacked HMW 7+8, LMW-2, and γ-45/ω-35 proteins which are important for pasta quality (Vincentini et al 2009).

Within hexaploid wheat, differences also exists. A comparison of European heritage and modern varieties for the production of α-9 epitopes implicated in celiac disease showed that 12 out of of 44 heritage collections produced low levels of the epitope, compared with only 1 out of 36 modern varieties (Van den Broeck et al 2010b). In another study, 2 modern genotypes had lower frequency of α-gliadin expression from the A-genome (15%), when compared to 5 landraces (29%) (Salentijn et al 2009).

Genetic linkages between loci for α-gliadins and HMW glutenins may explain why some modern varieties contain more celiac T-cell epitopes. Many modern varieties have been bred for increased HMW glutenin content, which improves bread baking quality when using common wheat and pasta quality when using durum (Kucek et al 2015). However, definitely not all heritage genotypes had low T-cell immuno-reactivity. Although average intensity of α-9 epitopes was higher in modern varieties, the most immuno-dominant variety identified by van den Broeck et al (2010b) was a heritage wheat.

In an evaluation of 16 ancient and modern wheats, one line of modern club wheat induced the second lowest in vitro T-cell response and IFN-γ release (Spaenij-Dekking et al 2005)

Prolamins from landraces emmer wheat L5540, L5558 and L5563 induced negligible responses in terms of cell proliferation and INF-g productionby intestinal T-cell lines from four celiac children (Vincentini et al 2009).

The Glia-α9 epitope is especially known as a major immunodominant epitope that can be recognized by the majority of CD patients (Vader et al. 2002; Camarca et al. 2009). The Glia-α9 epitope sequence (αI) is part of the proteolytic-resistant 33-mer in α-gliadins that has a strong T-cell stimulatory effect (Shan et al. 2002; Shan et al. 2005). The Glia-α20 epitope, which is used in this study as a technical reference, is a minor epitope that is recognized by a minority of patients.

Cadenza and CGN08327 hat the lowest content of both Glia-α9 and Glia-α20 epitope, and whereas some varieties were low in Glia-α9 but medium to the Glia-α20, including ‘Minaret’ (CGN19307), ‘Weissahr Rotkorn Binkel’ (CGN04210), ‘Rouge de la Gruyere’ (CGN08315), CGN12071, and ‘Pyrothrix 28’ (CGN04236) (van den Broeck et al 2010).

Patients reaction to wheat and different wheat varities is not only an effect of the content of different specific epitodes. The gliadins, including the allergenic peptides within them, create tight and compact structures that can be difficult to digest (Arentz-Hansen et al. 2002). The gluten formation may therefore affect the immuno-reation, and the targeted breeding effort to improve baking quality by improved gluten formation may have a negative side effect on wheat allergy and celiac disease.

Normally, molecules with a radius of more than 3.5kDa cannot pass from through the gut and into the blood stream, unless the tight junctions are opened. Antigens such as proteins, peptides and other molecules are larger than 3.5kDa, and therefore cannot cause allergy, autoimmune diseases etc unless passing through the tight junctions (Fasano 2012).

Gut infections with bacteria and vira causes increased water release into the intestine resulting in diarrhoea. It is still unclear if this reaction is an attempt of the body to flush out potential pathogens, or if it is a process driven by bacteria and vira as a means to invade the body. Whatever, this release of water through the intestine tight junctions are regulated by the protein zonolin. The presence of gliadin in wheat seem to mimic certain vira, and affects the gut permeability by triggering zonulin (Clemente et al 2003, Drago et al 2006, Fasano 2012). Therefore, allergens and neuropeptides from wheat and from other foodstuff consumed with the wheat, can therefore pass through the tight junctions into the blood stream and course food allergies and other disorders incl. celiac disease. The chemokine receptor CXCR3 is the target intestinal receptor for gliadin, and two α-gliadin 20mers (QVLQQSTYQLLQELCCQHLW and QQQQQQQQQQQQILQQILQQ) bind to CXCR3 and release zonulin (Lammers et al 2008). The CXCR3 receptor is over-expressed in celiac patients releasing extra zonulin (El Asmar et al 2002).

Celiac disease is triggered by the ingestion of gliadin fraction of gluten in genetically susceptible subjects having the HLA-gene with subsequent immune reaction leading to small intestine inflammation. Both celiac and type-1 diabetic patients have increased zonulin levels and over expression of one of the HP2 gene encoding for zonulin production.

## ATI

One of the non gluten proteins relevant for human health are the ATIs (α-amylase-trypsin inhibitors) which are albumin proteins, surrounding starch molecules in the endosperm, protecting them from digestion by insects and mammals including humans, and may regulate starch metabolism during seed development and germination (Guo et al 2012). Wheat ATIs are a family of compact, highly disulphide-linked and protease-resistant proteins. Complete sequencing of the genome of modern hexaploid wheat revealed up to 19 different ATI-encoding genes (Altenbach et al 2011).

The role of ATIs are to regulate seed dormancy, and to prevent protease and amylase enzymes released by pathogens and predators in digestion of the wheat seed. By plant breeding, the attempt to prevent pre-harvest sprouting and increase pest resistance may have selected for increased content or activity of ATIs. It has been found that ATI bioactivity is higher in modern hexaploid wheat, rye, and barley, while bioactivity was lower in older wheat variants, including spelt, emmer, and Einkorn (Zevallos et at 2017, Dupont et al 2011).

Heyden 2018 found huge differenced in ATI content wheat varieties, and lowest content in the varieties Pizza, Ludwig, Scaro, Naturastar and Goldritter.

While not being the trigger of celiac disease it self, cereal ATIs are contributors to celiac disease and fuel inflammation and immune reactions in other intestinal and non-intestinal immune disorders. ATIs engage the TLR4-MD2-CD14 complex and lead to up-regulation of maturation markers and elicit release of pro-inflammatory cytokines in cells from both celiac and non-celiac patients. ATIs from wheat and other gluten-containing cereals are nutritional activators of innate immune responses via TLR4 in the intestine (Zevallos et at 2017).

ATI thus has a triple role as an anti-nutrient in wheat. Ingestion of ATIs contributes to the activation of innate immune cells in low-level pre-existing small intestinal and colonic inflammation. It is an allergen itself causing baker's asthma (prevalence of up to 8% among bakers (Walusiak et al 2004)), and being an inhibitor of relevant enzymes, it prevents the proper digestion of other anti-nutrient proteins and carbohydrates. ATI fractions 0.19 and 0.38, which are classified based on fractionation in chloroformand electrophoretic mobility, were found to be active against α-amylase in human saliva and pancreas, respectively (Choudhury et al 1996)

## Phytin

Phosphorous supply is essential for early root development in plants. To ensure ample supply of phosphorous, plants store up to 50-90% of the phosphorous in phytate (Loewus 2002; Kumar et al. 2012). Phytate exists in the forms of free acid, phytic acid, and phytin (Lori et al., 2001) and is mainly found in the bran. Phytate P is poorly available to animals and can reduce the digestibility of other nutrients and the performance of animals owing to its anti-nutritional effect (Woyengo and Nyachoti 2013). Like ATIs, phytate inhibits amylase (Deshpande and Cheryan 2006, Cawley and Mitchell 1968).

As phytate is a poly-anionic molecule, it has the capacity to chelate positively charged cations, especially calcium, iron and zinc. Furthermore, it compromises the utilization of other dietary nutrients, including protein, starch and lipids. Phytate depresses protein/amino acid utilization and decrease protein solubility, enzymatic activity and proteolytic digestibility (Lillford and Wright, 1981; Deshpande and Damodaran, 1989; Urbano et al. 2000).

Trypsin is the most critical pancreatic protease, because it activates the other proteases. (Homer et al 2015). Phytate–protein complexes are less likely digested by proteolytic enzymes (pepsin, trypsin, chymotrypsin) and also other pancreatic digestive enzymes like lipase and alfa-amylase might be inhibited by phytate (Macholz, 1986; Caldwell, 1992). Kumar et al (2010) conclude that this inhibition may be due to the non-specific nature of phytate–protein interactions and the chelation of Ca-ions, which are essential for the activity of trypsin and alfa-amylase.

Like ATI's, phytate is an essential part of the dormancy of wheat kernels, and thereby in positive trait of resistance to pre-harvest sprouting and retaining a high Hagsberg Falling number. At the same time, both phytate and ATI's a strong anti-nutrients with both direct effect on nutrition and a secondary effect of inhibiting proper digestion of other anti-nutrients such as food allergens.

## Neuro- and phycological effects of wheat consumption

Milk contains casein, and peptides from undigested caseins are called exorphins, as they have endorphin like effects in the body and brain. The addictive properties of milk were arguably designed by evolution to gratify and pacify suckling babies. The gut of newborns is highly permeable—not only to the mother's antibodies as an aid to their still immature immune system, but also to milk opioids (Teschemacher,2003). The opioids in bovine milk are 10 times stronger than those in human milk (Herrera-Marschitz et al., 1989).

α-gliadins in wheat can be degraded to a collection of opioid-like polypeptides called exorphins including gliadinomorphin-7 in the gastrointestinal tract (Trivedi et al 2014) and the opioids in wheat are even stronger than those in bovine milk (Zioudrou et al. 1979). The potential connection

between a malfunctioning opioid system and eating disorders such as anorexia has also been documented (Yeomans and Gray, 2002).

The presence of antibodies against gluten is found in 87% of unmedicated autistic children vs. 1% of normal children (Cade et al., 2000), and have also been found much more often in schizophrenia patients than in the general population or in controls (Jackson et al. 2012a). In several countries, hospitalization rates for schizophrenia during World War II dropped in direct proportion to wheat consumption due to shortages. In the United States, where over that same period the consumption of wheat rose rather than diminished, such rates increased instead (Dohan, 1966a,b). Polynesia previously had low consumption of wheat, but schizophrenia rose dramatically (roughly, from 1 out of 30,000 to 1 out of 100) when Western grain products were introduced (Dohan et al.,1984). Abnormally high levels of exorphins from either wheat and/or milk have been found in the urine (Hole et al., 1979) and blood (Drysdale et al., 1982) of schizophrenia patients and in the urine of autistic children (e.g., Sokolov et al., 2014; but see Cass et al., 2008). Schizophrenia patients kept on a grain-and-milk-free diet worsened on 30 out of 39 behavioral measures when exposed to a gluten containing diets, and recovered when it contained soy flour in stead (Singh and Kay, 1976).

Antibodies against the brain, triggered by gluten, can cause severe neurological dysfunctions whether or not one is celiac (Hadjivassiliou et al., 2010). GABA is the prime inhibitory neurotransmitter, whose dysregulation is implicated in both anxiety and depression. In vitro, antibodies against gluten removed from human blood attack cerebellar proteins and components of the myelin sheath that insulates nerves (Vojdani et al., 2014), and also attack an enzyme involved in the production of GABA. This may explain the phycological effect of wheat consumption coursing anxiety and depression. In the blood of blood-donors, antibodies against wheat or milk and antibodies against these brain-relevant substances have been found to be simultaneously elevated, consistent with the presence of a cross-reaction between wheat allergy and psychological disorders (Vojdani et al., 2014).

Zonulin increases the permeability not only of the intestinal wall as described above, but also of other no less interesting barriers such as the blood-brain barrier. A toxin mimicking zonulin is actually being studied for its ability to enhance delivery to the brain of drugs such as anticancer agents (Karyekar et al., 2003).

When wheat starch are digested, blood sugar increases resulting in an increase in insulin production. However, exorphins in wheat further increases insulin production (Fukudome et al 1995) contributing to the negative effect that wheat has development of diabetes-2 and obesity.

## Conclusion

Wheat is a rich source of energy and protein, and has unique baking quality. Wheat also has a range of beneficial phytochemicals, including antioxidants and dietary fibres. However, wheat also has some problematic allergens and anti-nutrients that need to be taken into account when used for human consumption.

Some people reacts when digesting wheat. About 1% develop the autoimmune celiac disease, 2.9% are allergic to wheat and based on blood test it is estimated that another 12% is potential allergic to wheat as antibodies IgE can be found in their blood samples. About 11% has IBS, a condition where the fructan content in wheat may course problems.

There are several reasons for wheat being so problematic in our diet.

First of all, wheat is the most consumed crop in the world and by far the most intensively studied. Therefore, we know more about the problems related to wheat consumption than we know about other less consumed and studied crops. At the same time, the impact of any problem related to wheat consumption is more significant, because wheat is such a widely used and consumed crop.

Like most other seed, the nutrients in the wheat grain is protected both by anti-nutrients to prevent pre-harvest germination and against pathogens and predators like humans, by a range of mechanisms. Phytate, ATIs and other substances prevent the proper digestion of carbohydrates and minerals, and also of proteins, some of which may trigger allergy, and autoimmune and psychological disorders. Most of these anti-nutrients can be diminished by some degree of pregermination or long time fermentation. The increasing prevalence of celiac disease and other wheat and gluten related disorders may be due to increased focus on maintaining high falling number in wheat, and reduced fermentation time in wheat and bread processing during industrialisation of the food industry.

One significant difference between wheat and other seed and crops is a peptide that has impact on the release of zonulin in the gut and opening of tight junctions. Therefore, allergens, neuropeptides and anti-nutrients from both wheat and from other food ingredients can pass the gut barrier into the blood stream, and also pass the brain-blood barrier. This may be the main reason to wheat seemingly courses more problems that many other foodstuffs.

## Potential for improving the health profile of wheat

There are huge differences between wheat varieties in their content of anthocyanins, carotenoids and soluble dietary fibres. Most of the beneficial properties and ingredients of wheat can therefore be improved further by plant breeding.

There are also differences between varieties concerning the content of certain anti-nutrients, including ATI, β-expansin and gliadin- and other gluten epitodes coursing celiac disease and other immunoreactions. Theoretically, it should therefore be possible to breed more safe wheat. However, more then 50 different peptides are identified in wheat which may course allergy or autoimmune reactions, and for example celiac disease is not triggered by only one epitode, but can be triggered by several different epitodes.

Another problem related to breeding safe weat is that there are interactions between different phytochemicals and properties in wheat.

A high content of dietary fibre is a positive trait, but the content of fructan is correlated with the general content of dietary fibres and may course problem for some consumers with IBS.

Increased amount of high molecular glutenins is essential for baking quality in particular elasticity, water uptake and gluten index, but formation of strong gluten structure decreases digestibility of the proteins, increasing the risk of immune triggering peptides in the gut.

The content of ATI and phytate can be decreased by plant breeding, but it may have negative effect on falling number resistance and therefore baking quality.

Breeding for reduced zonulin triggering effect seems to be a trait that will have a positive horizontal effect on most of the antinutrient effects possibly without interacting with othertraits. However, little is known about the differences between varieties when it comes to zonulin triggering effects. Therefore, a screening of wheat varieties should be the starting point of a breeding program for this trait.

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