Gluten Opioids: Immune Dysfunction, and Mood Updated: SEPT 2020

Erik Vose, NMD

> *Disclaimer*: “Gluten-free” does not necessarily mean healthy. The term has become a fad and simply means: without gluten in the diet. It can indicate eating **anything else,** which may or may not be healthy for each individual. An individualized diet is the most successful strategy for an individual's health - this statement is based on modern as well as traditional medicine. Health care practitioners can be extremely valuable in helping individuals with chronic health issues develop a successful diet strategy. This document simply highlights one element of a healthy diet for individuals with chronic conditions such as autoimmune disease, digestive symptoms, and neurological or mood complaints, and is based on the principle of the exclusion of gluten as a means to see if this would be helpful. What do you have to lose by trying a gluten-free diet? Many have argued that eliminating gluten may result in nutrient deficiencies, and that excluding a particular common food may result in malnutrition if other foods are not available. As a result, please see the “Healthy, balanced, individualized diet guidelines” document provided by this author for strategies on avoiding nutrient deficiencies when excluding gluten from the diet.

INTRODUCTION TO OPIOIDS WITHIN GLUTEN

Wheat, arguably the most common food in the world, and its many varieties along with several other grains (rye, spelt, barley, triticale) contain a protein called gluten. The health related consequences of gluten are increasingly becoming obvious through an expanding scope of medical studies looking beyond simple celiac disease into what has now been termed “non-celiac gluten sensitivity” (NCGS). Medical professionals worldwide are publishing papers on the manifestations of gluten sensitivity outside of the digestive tract, where gluten is traditionally and undeniably identified as a trigger of an autoimmune disease called celiac disease. Celiac disease is a process involving the destruction of the digestive tract, malabsorption of nutrients, chronic and severe bowel symptoms, with potentially fatal outcomes if gluten is not eliminated. Now it is clear that **most people with gluten sensitivity do not have celiac disease**, and NCGS can still result in digestive, immune, and neurological symptoms.

The gluten protein is unique in its applications in food science as a strong binding protein in wheat flour that gives bread unique elastic consistency hardly matched by gluten-free products. Pizza dough and baked goods made without the use of gluten containing grains is usually very easy to identify. It may be said to be flat, more crumbly, or simply “grainy.” As a result, higher-gluten containing forms of wheat (and other gluten-containing grains) have been selectively developed over centuries through both modern and ancient agricultural methods. The gluten content of wheat has been steadily increasing, and perhaps for another reason as well. Gluten’s structure contains amino-acid sequences that trigger opioid receptors in the human digestive tract and nervous system resulting in an mild opioid-like addiction.

Wheat wasn’t always a common food protein, but since its incorporation into human food it has seen nearly unparalleled popularity. Researchers now understand this may be due the structure of gluten as it is partially digested resulting in the release of opioid receptor activating peptide sequences, referred to by researchers as *gluteomorphins* and *gluten exorphins*, or more specifically *gliadomorphins* when from the gliadin region of wheat protein. These opioid activating amino-acid sequences are now understood to cause dysregulation of the natural opioid system which influences digestion, mood, and the immune system. In severe cases these opioids contained within gluten can contribute to severe neurological and psychiatric symptoms.

Gluten Opioids: Immune Dysfunction, and Mood Updated: SEPT 2020

Erik Vose, NMD

GLUTEN IS DIFFICULT TO DIGEST

The term gluten represents a combination of proteins that make up the majority of the protein found in wheat. The group of proteins includes glutenins and gliadins, each with unique structures associated with different disease processes. As the primary protein found in wheat seeds, gluten's primarily role is thought to be storage of energy for plant growth after germination. Besides being generally resistant to breakdown (hydrolysis), gluten itself has been shown to inhibit the very digestive enzyme responsible for its own digestion in the human digestive tract (dipeptidylpeptidase IV). This is further complicated that when wheat is consumed, the high content of carbohydrates stimulates the human digestive tract to increase the pH of the intestines (for carbohydrate digestion) which results in the deactivation of protein digesting enzymes.

Wheat also contains complex carbohydrates called "FODMAPS" which are speculated to be another reason for NCGS. FODMAPS are so called because the term is an acronym for a group of fermentable carbohydrates that require more intensive digestion focused on carbohydrate break-down and absorption, often resulting in the development of bacterial growth due to poor absorption. In sensitive individuals (eg. with poor digestion), FODMAPS are associated with a variety of digestive symptoms from chronic gas and bloating to irritable bowel syndrome, anxiety, or even autism.

Together these qualities of wheat make it very difficult to digest, resulting in bacterial overgrowth, with an immune response that follows to regulate the bacteria. Inflammation then occurs as the immune system becomes active to regulate the digestive tract bacteria, which causes swelling of the tissues around the digestive tract. Once this occurs, the digestive tract becomes more permeable and food particles as well as bacteria byproducts can leak into the bloodstream and further activate the immune system.

This process is termed intestinal permeability (aka "leaky gut") and can result in immune responses to foods and bacteria that are ingested. The end result is triggering symptoms of chronic disease as a result of eating common foods such as wheat, dairy, eggs, and anything else that is eaten commonly. The end result is only worsened by the dysregulation of the natural opioid receptor system by amino-acid sequences within the gluten protein that would normally regulate the immune and nervous system.

GLUTEOMORPHINS: GLUTEN EXORPHINS AND GLIADINOMORPHIN-7

As early as 1992 opioids in wheat were identified using enzymes secreted during the human digestive process naturally, along with other opioids that were discovered through the use of enzymes from bacteria found within the human digestive tract. Once released through the complex digestive process, these opioids trigger a variety of changes directly and indirectly in the body. The effect varies based on individual capacity for digestion, opioid susceptibility, permeability of the gut, level of stress, and lifestyle factors for natural opioid productions such as exercise, sleep, and social support. Together these complex factors represent the combined genetic, immune and bacteria interactions as risk factors for gluten sensitivity of all kinds.

Gluten Opioids: Immune Dysfunction, and Mood Updated: SEPT 2020

Erik Vose, NMD

The 6 distinct gluten opioids, collectively referred to as gluteomorphins are:

- Gluten exorphin A4 (Gly-Tyr-Tyr-Pro-Thr) and A5 (Gly-Tyr-Tyr-Pro) arise from glutenin structures. Exorphin A5 is highly selective for the delta-opioid receptor and is associated with the mu-opioid receptor as well, and is found in abundance in the structure of glutenin (15 times per molecule). Exorphin A5 when ingested orally has been shown to exhibit pain relieving and memory/learning changes in mice in both the peripheral and central nervous system, suggesting effects in the brain directly.
- Gluten exorphins B4 (Tyr-Gly-Gly-Trp-Leu) and B5 (Tyr-Gly-Gly-Trp) arise from gliadin structure. Exorphin B5 is a potent trigger for enkephalins sharing the exact same structure as is naturally occurring in the body.
- Gluten exorphin C (Tyr-Pro-Ile-Ser-Leu) occurs during the natural digestion process of wheat with activity on both delta- and mu-opioid systems. Interestingly, this structure is not found in either glutenin or gliadin and is thought to arise from another protein in wheat.
- Gliadinomorphin-7 (Tyr-Pro-Gln-Pro-Gln-Pro-Phe) arises from gliadin structure with distinct effects on the delta and mu opioid receptor.

As gluten opioids are digested, the opioid receptor triggered by exorphin A5 stimulates insulin release and improves glucose balance. Similarly, prolactin levels were shown to elevate following gluten intake and improve with gluten elimination in sensitive individuals. Interestingly, many of these effects described are inhibited by naloxone (naltrexone) which is an established, evidence-based treatment for autoimmune disease.

These effects become more significant with the knowledge that these opioids have profound influence on the immune system, affecting white blood cells movement and response to infections. Furthermore, there is considerable cross reactivity between the various types of opioids in the brain and the different opioid receptors.

OPIOID RECEPTOR REVIEW

Opioids made within the body (endogenous opioids) are naturally occurring amino-acid sequences that activate opioid receptors throughout the digestive tract, the immune system, and the nervous system resulting in a wide array of effects. The endogenous opioids fall into three categories, either endorphins, enkephalins, or dynorphins. Together these natural opioids regulate one another and with overstimulation of one type of opioid receptor, the body adapts to find balance by increasing its opposing type. Additionally, studies show that many of the naturally occurring opioids in the body will cross react with more than one opioid receptor type.

- Endorphins bind to mu-opioid (μ) receptors to modulate acute pain, which is how morphine works, resulting in a variety of other changes to the body as well as an increased feeling of well-being.
- Enkephalins bind to the delta-opioid (δ) receptors modulate chronic pain, and reduce the effects of stress on the nervous system.
- Dynorphins bind to the kappa-opioid receptor (*κ*) are a more recently discovered type of natural opioid that are released under stress to modulate pain and produce negative

emotional states, such as anxiety, shame and dysphoria. Addictive behaviors have been associated with dynorphin induced kappa-opioid receptor activation.

IDENTIFYING AND ELIMINATING GLUTEN IN THE DIET

Individuals with the most resistance to eliminating gluten may be the most to gain from such a trial. After 4 weeks of 100% gluten elimination, patients with sensitivity to gluten can expect to see improvements in their condition. These improvements may not be obvious if other factors are making symptoms worse, such as new or increased stressors, other dietary or lifestyle changes that are detrimental to health. The real test becomes a reintroduction of gluten into the diet. If patients feel they have seen no improvement in their symptoms after 4 weeks of 100% gluten elimination, at that time they may be able to try eating gluten again consistently for 2 weeks. After the two week “challenge” phase of this elimination-challenge diet they can determine if symptoms have been significantly worsened. Some conditions such as autism spectrum disorder or multiple sclerosis may not be able to use this method as the elimination of gluten enables other therapies to work better, and may need longer time.

If gluten is not completely eliminated, and some sources remain, the degree of improvement in symptoms may range based on the frequency and quantity of gluten. Typically it will take upto 7 days before improvements in chronic symptoms are noticed after stopping eating gluten. Generally symptoms related to digestion may improve after 1-2 days with more regular digestion and less symptoms.

TESTS AVAILABLE

Antibody testing in the blood, stool, and saliva are available to check for evidence of gluten sensitivity. However due to the complex interactions between gluten, bacteria in the gut, and the body, the best test is to eliminate it for 1 month to see if it works for you. You may be able to start seeing improvements within just 1 week.

One may ask themself, what do I have to lose by trying this out?

For a reference on the various sources of gluten, please visit:
https://celiac.org/gluten-free-living/what-is-gluten/sources-of-gluten/

SOURCES

Balakireva AV, Zamyatnin AA. Properties of Gluten Intolerance: Gluten Structure, Evolution, Pathogenicity and Detoxification Capabilities. *Nutrients*. 2016;8(10):644. Published 2016 Oct 18. doi:10.3390/nu8100644
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5084031/

Fukudome S, Yoshikawa M. Opioid peptides derived from wheat gluten: their isolation and characterization. FEBS Lett. 1992 Jan 13;296(1):107-11. doi: 10.1016/0014-5793(92)80414-c. PMID: 1309704.
Available from: https://febs.onlinelibrary.wiley.com/doi/epdf/10.1016/0014-5793%2892%2980414-C

Gluten Opioids: Immune Dysfunction, and Mood Updated: SEPT 2020

Erik Vose, NMD

Fukudome S, Yoshikawa M. Gluten exorphin C. A novel opioid peptide derived from wheat gluten. FEBS Lett. 1993 Jan 18;316(1):17-9. doi: 10.1016/0014-5793(93)81727-h. PMID: 8422933.
Available from: https://febs.onlinelibrary.wiley.com/doi/epdf/10.1016/0014-5793%2893%2981727-H

Losurdo G, Principi M, Iannone A, et al. Extra-intestinal manifestations of non-celiac gluten sensitivity: An expanding paradigm. *World J Gastroenterol*. 2018;24(14):1521-1530. doi:10.3748/wjg.v24.i14.1521
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5897856/

Petra AI, Panagiotidou S, Hatziagelaki E, Stewart JM, Conti P, Theoharides TC. Gut-Microbiota-Brain Axis and Its Effect on Neuropsychiatric Disorders With Suspected Immune Dysregulation. *Clin Ther*. 2015;37(5):984-995. doi:10.1016/j.clinthera.2015.04.002
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4458706/

Pruimboom L, de Punder K. The opioid effects of gluten exorphins: asymptomatic celiac disease. *J Health Popul Nutr*. 2015;33:24. Published 2015 Nov 24. doi:10.1186/s41043-015-0032-y
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5025969/

Roszkowska A, Pawlicka M, Mroczek A, Bałabuszek K, Nieradko-Iwanicka B. Non-Celiac Gluten Sensitivity: A Review. *Medicina (Kaunas)*. 2019;55(6):222. Published 2019 May 28. doi:10.3390/medicina55060222
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6630947/

Takahashi M, Fukunaga H, Kaneto H, Fukudome S, Yoshikawa M. Behavioral and pharmacological studies on gluten exorphin A5, a newly isolated bioactive food protein fragment, in mice. Jpn J Pharmacol. 2000 Nov;84(3):259-65. doi: 10.1254/jjp.84.259. PMID: 11138726.
Available from: https://www.jstage.jst.go.jp/article/jjp/84/3/84_3_259/_pdf/-char/en

Trivedi MS, Shah JS, Al-Mughairy S, et al. Food-derived opioid peptides inhibit cysteine uptake with redox and epigenetic consequences. *J Nutr Biochem*. 2014;25(10):1011-1018. doi:10.1016/j.jnutbio.2014.05.004
Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4157943/