TRANSFORMATION

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BIOCHEMICAL FATE OF UNDIGESTED PROTEINS IN THE GI TRACT

Proteins constitute an indispensable group of macromolecules that need to be steadily provided to the human body. Proteins provide the amino acids for cell regeneration and synthesis of various biomolecules as well as nitrogenous compounds that are incorporated into the synthesis of nucleic acids. In fact, there is no bio-molecular reaction in the body that does not involve either a protein or a molecule synthesized by proteins.

In order to reach the various cells in the body, the ingested proteins must be digested (hydrolyzed). Although the human body can synthesize certain amino acids (non-essentials), there are also amino acids that must be regularly provided by the diet (essentials). In fact, even the amino acids that could be synthesized by the body rely on an adequate complete protein in the diet to ensure their synthesis.

In order to understand the biochemical fate of proteins in the gastrointestinal tract, a brief review of their molecular structure is important. Proteins are molecules made up of a sequence of amino acids linked together by a specific type of chemical bond called a peptide bond. This peptide bond is an amide linkage between the functional alpha carboxyl of one amino acid and the functional alpha amino group of another amino acid. This bond is what needs to be broken (hydrolyzed) in order to release the individual amino acids so that they could be absorbed within the intestinal cells.

As discussed in previous articles (***Dr. M's Science Notes***, vol 6 "Food Proteins," and vol 3 "Proteolytic Enzymes: Applications and Benefits"), proteins in the diet must be carefully selected based on their complete amino acid composition, regularly provided, and their digestibility ensured within the GI tract. Under normal conditions, ingested proteins are denatured in the stomach by hydrochloric acid, predigested by pepsin, and further hydrolyzed within the small intestine by various enzymes such as trypsin, chymotrypsin, elastase, carboxypeptidases, and aminopeptidases. This sequential action of the enzymes is well orchestrated by various gastric and intestinal secretions such as hormones, other bioactive peptides, and neural inputs. Upon normal hydrolysis of the proteins, the end products are single amino acids, dipeptides, and tripeptides that could all be absorbed into the enterocytes via an active transport mechanism.

This set of events leading to the bioavailability of amino acids does not occur perfectly in most cases. There are several factors that could hinder the proper physiological processes of digestion and absorption. These factors can be genetic, developmental, and environmental. They include availability of breast milk, early diet and weaning time, adult dietary composition, diseases, medications, alcohol, smoking, excess levels of the stress hormone cortisol, imbalances in the autonomic nervous system, environmental pollutants, and various other factors.

These inadequacies in the functioning of the digestive system lead to impaired protein hydrolysis and amino acid absorption. As a result, there will be protein fragments or peptides with various lengths (i.e., various number of amino acids) that remain in the gut for a relatively longer time than physiologically normal. Ultimately, these undigested proteins, amino acids, and other nitrogenous compounds will also move into the large intestine.

Biochemically, these residual proteinaceous compounds and amino acids within the lumen of the small intestine and large intestine will undergo various fates within the GI tract. Specifically, they will react with the cellular environment in the GI tract and also serve as nutrients to the microflora. The two main biophysiological fates of undigested proteins and their derivatives in the gastrointestinal tract therefore are:

- Bioactivity, including allergic reactions
- Microbial metabolism

BIOACTIVITY OF UNDIGESTED OR PARTIALLY DIGESTED PROTEINS

As discussed above, proteins are made up of amino acids. Every amino acid has an amino group and a carboxyl group that are both attached to one carbon atom (the alpha carbon). There is also a side group attached to the alpha carbon that differentiates among the various amino acids. In cases of impaired hydrolysis, the proteins may be intact or partially intact.

Depending on the nature of the protein and the level of hydrolysis it has undergone, the residue in the lumen of the GI may have some bioactivity. Bioactivity is defined here as any cellular response or molecular action resulting from a peptide or protein fragment. For instance, these protein fragments may act as hormones, signaling molecules, growth factors, neuropeptides, inhibitor or activator molecules, or many other active molecules. Upon partial hydrolysis, a simple structural protein may generate various peptides. Some of these peptides may have amino acid sequence similar to a neuropeptide or other bioactive peptide. Some of these new peptide molecules derived from an otherwise completely different protein may now stimulate nerve endings and elicit a biological response within the surrounding tissues or in a systemic manner within the body.

Some bioactive peptides can be as small as two amino acids or as large as several amino acids linked together. The physiological and medical consequences of this partial or impaired digestion are considerable. For instance, crystalline is a dipeptide (TYR-GLY) that is found in the pituitary gland and has been shown to elicit opioid-like effects in animals and possibly in humans. Another small peptide called kyotorphin (TYR-ARG) derived from the brain appears to have an analgesic effect. The possibility of generating these dipeptides during digestion is very high, as those two amino acids are frequent among proteins.

There are also several peptides generated from the partial digestion of the milk protein casein. Some of these peptides are commonly referred to as casomorphins because of their morphine-like effects. Some of the casomorphin peptides could be as small as three amino acids (Human beta-casomorphin TYR-PRO-PHE) or as large as seven or more amino acids (Human beta

casomorphin TYR-PRO-PHE-VAL-GLU-PRO-ILE or Bovine beta casomorphin TYR-PRO-PHE-PRO-GLY-PRO-ILE). There is another fragment called alpha casein derived from the partial hydrolysis of casein that is made up of only six amino acids (ARG-TYR-LEU-GLY-TYR-LEU). It is considered to be one of the most potent opioid-like peptides.

Another common protein source of bioactive peptides is wheat gluten. The partial digestion of wheat gluten yields an opioid-like peptide (TYR-PRO-ILE-SER-LEU). Another partially digested wheat peptide (ARG-PRO-GLN-GLN-PRO-TYR-PRO-GLN-PRO-GLN-PRO-GLN) appears to be very active in the etiology of Celiac disease. Other peptides derived from wheat have been specifically shown to activate T cells and induce large secretions of interferon gamma.

Undigested proteins and peptides remaining in the lumen could also act as antigens and illicit various immune responses and allergic reactions. Under some conditions, they could damage the homeostatic integrity of the intestinal mucosa lining, thereby increasing passive intestinal permeability (i.e., leaky gut syndrome). Thus, molecules of various lengths could easily pass from the lumen into the blood circulation and create a systemic load on the immune system. Many inflammatory bowel diseases result from such uncontrolled intestinal permeability of molecules.

Although the examples above focus on casein and wheat, any protein can be a culprit source if there is maldigestion. Even a small peptide could have a physiologically and medically significant impact on the body. In fact, even single amino acids could induce some biological action.

As discussed in previous articles (see ***Dr. M's Science Notes***, vol. 1 - "Nutrient Acquisition: The Foundation of Wellness"), nutrient acquisition that is ensured with the intake of effective supplemental digestive enzymes could help prevent the presence and/or persistence of undigested proteins, thus alleviating any of their potential health risks.

The effects of the various peptides could be beneficial or harmful. This is regardless of whether they are endogenous to the body or resulting from incomplete digestion. Some of the peptides have been shown to induce behavior and neurological changes, stimulate secretions of various glands and tissues, affect cellular growth, mimic other hormones, and affect many other functions. This represents an area of intense scientific research to determine the impact of nutrients on the body especially in this era of progress made in studies related to nutritional genomics.

MICROBIAL METABOLISM OF UNDIGESTED, UNABSORBED PROTEINS AND AMINO ACIDS

The large intestine hosts most of the 400-500 species of microorganisms in the GI tract. Under normal conditions, the microbial count is relatively very low in the stomach and the upper part of the small intestine. The count is slightly higher in the ileum and increases exponentially in the large intestine. Many of the microorganisms in the GI tract maintain a symbiotic relationship with the human host and among themselves. Other organisms that are potentially pathogenic are "kept in check" under normal conditions by the friendly organisms commonly referred to as probiotics.

All food residues that are not digested and/or absorbed along with dead GI tract cells and bacteria are ultimately processed into a form to be eliminated. During the process of feces formation, the microflora undertake considerably complex series of biochemical reactions, using all of the nutrients that reach the large intestine for their survival. It is during these reactions that many beneficial interactions with the human host take place, leading to a stable and healthy co-habitation between host and microorganisms.

This balance could nevertheless be disrupted by various factors including the excess discharge of proteins, peptides, amino acids, and nitrogenous compounds into the large intestine as well as the disproportionate distribution of "potentially pathogenic" organisms versus friendly organisms. Thus, when these conditions of poor digestion/absorption and imbalances in the microflora occur, the metabolites formed could overwhelm the body and set the terrain for acute and/or chronic health challenges.

Using proteins, amino acids, and nitrogenous compounds as biochemical substrates for their metabolism, microorganisms perform a combination of some key reactions. The various metabolic reactions are outlined below, and their byproducts may have an impact on the host health.

Further Hydrolysis of Undigested Dietary Proteins

The proteinaceous compounds that reach the large intestine include undigested dietary proteins, dead cells from the gut, and dead microorganisms. The microflora in the large bowel therefore proceeds to hydrolyze the proteins in order to release amino acids. Since some of the organisms cannot synthesize and/or secrete proteolytic enzymes, they depend on other organisms to hydrolyze the proteins. The longer the transit time in the large intestine is, the more protein putrefaction takes place, resulting in the formation of unpleasant gases.

Deamination of the Amino Acids

Without proper digestion/absorption of proteins and amino acids, a biochemical process results in the formation of ammonia, carbon dioxide, hydrogen, and various organic acid by-products. Depending on the side chain of the amino acid attached to the alpha carbon, the organic acids produced may include acetic, propionic, butyric, pyruvic, succinic, isocaproic, isovaleric, isobutyric, and 2-methyl N-butyric. In fact, because the formation of some of these organic acids is mostly the result of bacterial proteolysis and deamination, these acids are used as diagnostic metabolites to assess the extent of protein digestion/absorption. The organic acids mostly used for these tests are those derived from branched chain amino acids and include isovaleric, isocaproic, 2-methyl N-butyric, and isobutyric. The higher the concentrations of these organic acids in stool sample, the more likely the patient does not have proper digestion/absorption of proteins and amino acids.

Other by-products of the amino acid deamination reactions include phenol, cresol, aryl acetic, aryl propionic, indolepropionic, indolelactic, indoleacetic, indole, skatole, and indican. These products are derived from the aromatic amino acids and could also be used to diagnose digestive problems as well as toxicity in the body. The use of these as toxicity markers is due to the fact that they could be easily absorbed into the blood circulation. Thus, high levels in the urine indicate some aspect of toxicity.

Decarboxylation of Amino Acids

This is a process that, along with deamination, is used by microorganisms to benefit from the amino acids that have been released from the proteins. The basic products of decarboxylation of amino acids include various amines and carbon dioxide. The amines most formed during this biochemical reaction of the organisms include putrescine, cadaverine, methylamine, ethylamine, histamine, tyramine, octopamine, agmatine, tryptamine, serotonin, quinaldic acid, 3-hydroxykynurenine, xanthenuric, 3-hydroxyanthranilic, and methyl mercaptans. Some of these are further metabolized to form piperidine and pyrrolidine. Many of these various amines have been shown to stimulate cell proliferation that, under excess conditions, could lead to tumor cells. Agmatine, for instance, has an insulin-like effect, and it is possible that under conditions of excess, it may

induce insulin resistance. The extent of these microbial reactions depends on the nature and levels of the nitrogenous substrates as well as the taxonomy of the flora.

Ammonia and Urea Metabolism

Ammonia is the main substrate for the microorganisms, as they derive it from the amino acids and incorportate into their metabolism for the synthesis of proteins for their growth and survival. The ammonia produced diffuses into the organisms. Using the energy derived from some of the organic acids produced by the deamination or fermentation of carbohydrates, the ammonia will be converted by the microorganisms into amino acids and incorporated into proteins.

The more ammonia formed by the bacteria, the higher the concentrations of ammonia that can also diffuse into the colonocytes and into the blood circulation of the host. Thus, while some ammonia is used by the bacteria, another portion is assimilated, potentially intoxicating the host. Constipation will only further increase the metabolic reaction times, promote the absorption of more fluid-laden ammonia and other metabolites into the human host, and help promote the formation and absorption of more secondary microbial metabolites that could harm the body.

Once in the blood circulation, the ammonia is passed into the liver where it is converted into urea to be eliminated in the urine or feces. However, as concentrations of ammonia in the blood that reaches the liver increases, the liver may become overwhelmed, leading to further health challenges. Also, as urea formed in the liver passes back into the GI tract, it could be further hydrolyzed by the organisms in the large intestine to form ammonia once again. The cycle continues, should the digestive and microflora conditions fail to function optimally.

The above reactions by microorganisms are normal in most cases in the human GI tract. However, it is the kinetics of the reactions as well as the higher levels of substrates and metabolites resulting from poor digestion and imbalance in microflora taxonomy that should be avoided in order to minimize any load on the body's detoxification systems and prevent the onset of chronic and degenerative diseases. As discussed above, nutrient acquisition and proper flora balance constitute key factors in maintaining good health, reducing the weakening effects of chronological age, and ensuring vitality.

CONCLUSION

Thus, as proteins constitute a necessary part of human diet, their hydrolysis within the GI tract must be optimized to avoid the health risks discussed above. More specifically, the problems discussed here are not due to protein in the diet, but rather to the inadequacy of their digestion. Additionally, it should be reiterated that any protein could present some of the problems discussed, and it is not only casein or gluten that could generate bioactive peptides with potential health concerns. More importantly, this discussion attempts to illustrate the importance of proteolytic enzymes as dietary supplements to enhance the digestion of proteins and ensure the bioavailability of amino acids.