The Great Plains Laboratory, Inc.

DPP-IV: A Key Enzyme in Food Sensitivities and Virtually All Human Physiology

Dipeptidyl Peptidase IV or DPP-IV is a critical enzyme that regulates a wide variety of physiological processes including eating, digestion, immune function, pain perception, growth, infection, and many others. This enzyme, which is present in all organs and the blood, starts or stops these processes by removing a two amino acid peptide from a variety of peptides and proteins from the free amino end of these molecules. Thus, growth hormone releasing factor (GHRF), which is secreted by the hypothalamus, stimulates the pituitary gland to release growth hormone until DPP-IV removes two amino acids from GHRF to inactivate it. Substance P, a nine amino acid peptide, mediates the perception of pain when released from injured tissue and continues to provoke pain until DPP-IV removes two amino acids from substance P, terminating the pain perception.

**DPP-IV and Side Effects of New Diabetes Drugs**

The function of DPP-IV has been a major target of new drugs called DPP-IV inhibitors that have been developed to control adult onset diabetes. These new oral drugs such as Januvia® (sitagliptin), Galvus® (vildagliptin), Onglyza® (saxagliptin), Tradjenta® (linagliptin), and many others are inhibitors of DPP-IV that cause persistence of peptides normally broken down by DPP-IV such as glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), that potentiate the effects of insulin and even increase the growth of insulin-producing cells in the pancreas. However, these DPP-IV inhibitors used to treat diabetes also cause the persistence of pain mediators usually deactivated by DPP-IV such as substance P. Therefore, it is not surprising that patients whose rheumatoid arthritis was under control, report severe joint pain, sometimes within one day of using these anti-diabetic drugs. Furthermore, stopping these drugs terminates pain and re-institution of the drug causes pain to return. Since substance P is a major factor in increasing anxiety, it is reasonable that these drugs may also lead to increased anxiety. A 2014 review found increased risk of heart failure with saxagliptin and alogliptin, prompting the FDA in 2016 to add warnings to the relevant drug labels. A 2018 meta-analysis showed that use of DPP-IV inhibitors was associated with a 58% increased risk of developing acute pancreatitis compared with placebo or no treatment. Since very low serum DPP-IV values are associated with suicidal depression, it would be wise to advise any patient using these diabetes drugs of this potential side effect.
DPP-IV and Dietary Sensitivities

Since DPP-IV inhibitors can cause pronounced side effects, it is logical that foods that are converted to DPP-IV inhibitors, through enzymatic digestion, may have pronounced effects on human functioning. The food proteins that have the highest amounts of these DPP-IV inhibitors are cow’s milk and wheat. Each of these proteins produces a peptide with five-seven amino acids with high opiate activity when digested as indicated below:

<table>
<thead>
<tr>
<th>Casomorphin</th>
<th>tyr</th>
<th>pro</th>
<th>phe</th>
<th>pro</th>
<th>gly</th>
<th>pro</th>
<th>ile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliadorphin</td>
<td>tyr</td>
<td>pro</td>
<td>gln</td>
<td>pro</td>
<td>gln</td>
<td>pro</td>
<td>phe</td>
</tr>
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</table>

Both of these opiate peptides can be broken down further by DPP-IV by removing the first four amino acids but the residual three amino acid peptides of both casomorphin and gliadorphin (amino acids five, six, seven of the peptides in the above diagram) are potent DPP-IV inhibitors that will inhibit the function of DPP-IV in regulating all of the other endocrine and immune functions of the proteins and peptides that are substrates of DPP-IV. Thus, a person with a diet high in gluten and casein might be much more subject to pain and anxiety if their substance P persisted for much longer periods of time due to the high amounts of potent DPP-IV inhibitors from gluten and casein. DPP-IV is a jack of all trades. The table below is a likely incomplete list of proteins and peptides that are regulated by DPP-IV.

<table>
<thead>
<tr>
<th>Procalcitonin</th>
<th>RANTES</th>
<th>Monocyte chemoattractant protein 3 (MCP-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyr-Melanostatin</td>
<td>Glucose-dependent insulino tropic peptide (GIP)</td>
<td>Eotaxin</td>
</tr>
<tr>
<td>Endomorphin-2</td>
<td>Growth hormone-releasing hormone (GRH)</td>
<td>Interferon-inducible protein 10 (IP-10)</td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Glucagon-like peptide 1 (GLP-1)</td>
<td>Insulin-like growth factor (IGF-1)</td>
</tr>
<tr>
<td>B-Casomorphin</td>
<td>Glucagon-like peptide 2 (GLP-2)</td>
<td>Procolipase</td>
</tr>
<tr>
<td>Trypsinogen pro-peptide</td>
<td>Granulocyte chemotactic protein-2 (GCP-2)</td>
<td>Interleukin-2 (IL-2)</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Stromal cell-derived factor 1a (SDF-1a)</td>
<td>Interleukin-1b (IL-1b)</td>
</tr>
<tr>
<td>Substance P</td>
<td>Stromal cell-derived factor 1b (SDF-1b)</td>
<td>1-Microglobulin</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Macrophage-derived chemokine (MDC)</td>
<td>Prolactin</td>
</tr>
<tr>
<td>Soymorphin</td>
<td>Monocyte chemoattractant protein 1 (MCP-1)</td>
<td>Trypsinogen</td>
</tr>
<tr>
<td>CLIP</td>
<td>Monocyte chemoattractant protein 2 (MCP-2)</td>
<td>Human chorionic gonadotrophin (HCG)</td>
</tr>
<tr>
<td>Gastrin-releasing peptide (GRP)</td>
<td></td>
<td>Peptide histidine-methionine (PHM)</td>
</tr>
<tr>
<td>Neuropeptide Y (NPY)</td>
<td></td>
<td>Gliadorphin</td>
</tr>
<tr>
<td>Peptide YY (PYY)</td>
<td></td>
<td>Amyloid beta-peptides</td>
</tr>
<tr>
<td>Aprotinin</td>
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</table>

One of the most remarkable features of milk sensitivity is the disease implications of the change of a variant in the milk protein casein due to a dietary fad beginning in the 1960s. At this time, a major dietary fad began which demonized high fat foods. Most of the dairy cows at the time produced a specific casein protein called casein A2 which was controlled by a specific single nucleotide polymorphism or SNP in the cow DNA. It was found that these dairy cows also produced milk with a higher fat content than cows that produced A1 or B casein. Because of this dietary fad, milk producers largely stopped raising dairy cows with the SNPs that produced casein A2 and switched to produce cows that made casein A1 or B milk. This genetic change brought about by artificial selections by farmers is unrelated to how cows are fed and how the milk is processed. The effects of this artificial selection of low fat, non-A2 casein cows appear to have caused huge health losses throughout the world. Countries who switched to non-A2 casein cows developed human populations with much higher incidence of juvenile diabetes, depression, schizophrenia, autism, cancer, and ischemic heart disease. Presumably the major reason for the increased disease incidences associated with increased intake of non-A2 casein is that peptide products of the digestion of A2 casein do not cause DPP-IV inhibition while non-A2 casein digestion products are potent DPP-IV inhibitors. Because of the increased knowledge of the benefits of A2 milk, different A2 milk brands are now available in supermarkets throughout the United States and many other countries.
Conditions Associated with DPP-IV Deficiency
DPP-IV deficiency is associated with a wide range of illnesses including many psychiatric illnesses, autoimmune diseases, digestive diseases, lung diseases, and cancer:

### Psychiatric Disorders
When DPP-IV activity was measured in the serum of 21 women with anorexia nervosa, 21 women with bulimia nervosa and 18 normal women, the DPP-IV activity was significantly lower in patients with anorexia nervosa and bulimia nervosa than in the normal controls. In the total study group, there were significant and inverse relationships between serum DPP-IV activity and the total scores on the Bulimic Investigatory Test, Edinburgh, the Eating Disorder Inventory (EDI), and the Hamilton Depression Rating Scale.

The diagnostic usefulness of serum DPP-IV in depression were assessed by enzymatic assays in serum samples from 240 unipolar depression (UD) patients and 264 matched controls, demonstrating much lower DPP-IV values in depressed patients with the lowest values occurring in patients with suicidal depression. Low DPP-IV is found in abstinent alcoholics. Table 2 is a summary of conditions associated with DPP-IV deficiency.

### Cancer
The role of DPP-IV in metastases of some tumors is remarkable. Melanoma cells express very limited DPP-IV but insertion of DPP-IV producing genes into these cells converts them into non-malignant cells. In Ewing sarcoma, patients with high DPP-IV had increased survival rates. In oral cancers, patients with oral cancer had significantly lower serum DPP-IV activities compared to normal controls. Furthermore, serum DPP-IV values increased in those patients who improved and declined in those whose disease worsened.

### Lung Disease
DPP-IV is significantly decreased in chronic obstructive pulmonary disease (COPD) compared to normals and its specificity is so high that it has been proposed as a diagnostic test for COPD.

### Alzheimer’s Disease
Beta-amyloid is a peptide found in Alzheimer’s disease. Indeed, the aggregates of amyloid beta peptides (Aβs) are regarded as one of the main pathological hallmarks of Alzheimer’s disease. It is an anti-microbial peptide that is active against Candida and it has been proposed that the deposits in the brains of patients with Alzheimer’s disease might be an attempt by the innate immune system to control brain Candida. Two of the peptides, Aβ40 and Aβ42 are substrates of DPP-IV. DPP-IV prohibits the fibrillation of peptides and promotes disaggregation of their pre-formed aggregates. The failure to clear amyloid brain deposits in Alzheimer’s disease might be another long-term side effect of the DPP-IV inhibitor drugs for diabetes.

### Pain Control and Arthritis
In serum as well as in synovial membrane from rheumatoid arthritis patients, DPP-IV activity or CD26 antigen levels were reduced compared to controls. The pain associated with fibromyalgia and arthritis is likely connected to higher amounts of substance P, a major pain mediator, in the blood. The excessive substance P, in turn, is likely due to decreased DPP-IV and explains increased arthritis pain experienced as a frequent side effect when the DPP-IV inhibitor anti-diabetes drugs are used.

### Other Conditions
Serum DPP-IV activity is decreased during pregnancy, in subjects with active Crohn’s disease, active systemic lupus erythematosus, active Wegener’s granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis. Berberine is a DPP-IV inhibitor, so this supplement should be discontinued at least 72 hours before phlebotomy when testing for DPP-IV. The HIV viral protein tat is a strong inhibitor of DPP-IV so individuals with active HIV infections may have low DPP-IV values. The inhibition of DPP-IV may be a factor in the immune deficiency caused by the HIV virus. Low values of DPP-IV are found in sepsis.
Recommended Supplements for DPP-IV Deficiency

Houston Enzymes’ TriEnza is a multi-enzyme, high DPP-IV peptidase formula, which aids in digestion of food proteins including gluten, casein, soy, starches, carbohydrates, sugars (including lactose), and fats. Their AFP Peptizyde product is also high in DPP-IV, but doesn’t include several of the other enzymes in TriEnza, and is sold at a lower price point. Both of these products are available from New Beginnings Nutritional at www.NBNUS.com.

References