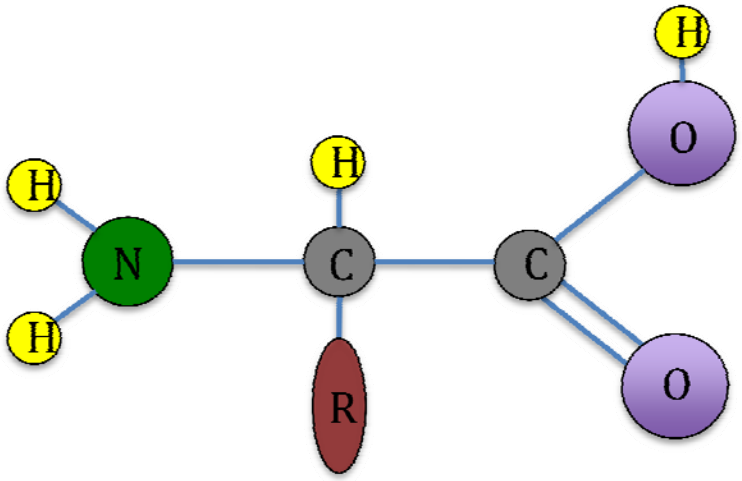
Amino acids are molecules containing an amine group (NH_2), a carboxylic acid (COOH) group and a side chain that varies. In an alpha amino acid, the amino and carboxylate groups are attached to the same carbon atom, which is called the α-carbon. The various alpha amino acids differ in which (R group) is attached to their alpha carbon.



These side chains can vary in size from just a hydrogen atom in Glycine to a methyl group in Alanine through to a large heterocyclic group in Tryptophan.

Amino acids are critical to life, and have many functions in metabolism. One particularly important function is as the building blocks of proteins, which are linear (straight) chains of amino acids. Every protein is chemically defined by this primary structure, while its unique sequence of amino acid residues, in turn define the three dimensional structure of the protein. Amino acids are linked together in varying sequences to form a vast variety of proteins. Amino acids are also important in many other biological molecules, and due to this central role in biochemistry, they are very important in nutrition.

Amino acids join together to form short polymer chains called peptides or longer chains called either polypeptides or proteins. These polymers are linear and unbranched, with each amino acid within the chain attached to two neighbouring amino acids.

Twenty-two amino acids are naturally incorporated into polypeptides and are called proteinogenic or standard amino acids. Of the twenty-two standard amino acids, eight are called essential amino acids because the human body cannot synthesize them from other compounds at the level needed for normal growth, so they must be obtained from food. However, the situation is quite complicated since cysteine, Taurine, Tyrosine, Histidine and Arginine are semiessential amino acids in children, because the metabolic pathways that synthesize these amino acids are not fully developed. The amounts

required also depend on the age and health of the individual, ***so it is hard to make general statements about the dietary requirement for some amino acids.***

Non-protein functions of Amino Acids: Besides building proteins, many amino acids are used to synthesize other molecules, for example:

Tryptophan is a precursor of the neurotransmitter seratonin. Almost 80% of the serotonin in a human body is found in the gut, where it is secreted and absorbed into the blood platelets, and helps regulate critical functions like blood cotting and wound healing. The remainder is synthesized in serotonergic neurons in the Central Nervous System, where it has various functions, including the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions including memory and learning.

Glycine is a precursor of porpyrins, which is the red pigment in blood.

Arginine is a precursor of nitric oxide, which is an important signaling molecule in Mammals. NO is one of the few gaseous signaling molecules known. It is a key vertebrate biological messenger, playing a role in a variety of biological processes. The (inner lining) of blood vessels uses nitric oxide to signal the surrounding smooth muscle to relax, thus resulting in what is called vasolidation which increases blood flow. Nitric oxide is highly reactive (having a lifetime of a few seconds), yet diffuses freely across our body's membranes. These attributes make nitric oxide ideal as a signaling molecule between adjacent cells as well as within a single cell. Effects include vasodilatation, modulation of the hair cycle, and penile erections (through its ability to vasolidate). Sildenafil Citrate, popularly known by the trade name *Viagra*, stimulates erections primarily by enhancing signaling through the nitric oxide pathway in the penis.

Nitric oxide (NO) contributes to vessel homeostasis by inhibiting vascular smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion to the endothelium. Humans with atherosclerosis, diabetes or hypertension often show impaired NO pathways.

Glycine and glutamine are precursors of nucleotides. **Nucleotides** are molecules that, when joined together, make up the structural units of RNA and DNA. In addition, nucleotides play central roles in metabolism. In that capacity, they serve as sources of chemical energy (adenosine triphosphate and guanosine triphosphate), participate in cellular signaling

PEPTIDES:
Peptides are short polymers formed from the linking, in a defined order, of α-amino acids. Hence depending on the number of amino acids, peptides are called di-peptides, tri-peptides, oligopeptides, etc. Proteins are multi peptide chains.

Small amino acid chain peptides, commonly known as oligopeptides are very easily transported through the intestinal, membrane. They are sometimes used as transport mechanisms for drugs.

Protein must be broken down to smaller and smaller peptides, and eventually an amino acid to perform it's functions. Dietary intake of peptides and amino acids, therefore, can be extremely beneficial.

Peptides are the most abundant compounds in the hypothalamus of the brain, and perform vital functions of communicating sensory impulses to the endocrine system (hormone producing glands). Peptide based hormone-releasing agents from the hypothalamus use the anterior pituitary to signal the thyroid gland, the adrenal cortex, the mammary gland, the ovaries & testicles and the growth hormone.

Understanding the mechanisms of the effect of peptides, and the types of peptides is a complex field, and is being studied extensively. Unfortunately, these studies are done in isolation and disregard the wholistic picture of the complex mechanisms, which exist in our marvelous bodily electrochemical system. Further, the studies are focused on promoting a particular amino acid, peptide or other neurotransmitter. While the results identify the final activity with the amino acid/peptide, the mechanism of transport of such critical amino acid/peptides to the final destination is a subject of major arguments. These arguments cast a shadow on the importance of nutritional supplements. Most doctors will tell you nutritional supplements "cannot hurt", but stop short of endorsing them. The reason is the lack of evidence that the active ingredients have been formulated in the correct form, that is, intermediates or ligands that can make the active ingredient available to the nervous or endocrine system of the brain.

At Pendura, we take a different approach. Our goal is to maximize benefits, not profits. We strongly believe that it is not enough to understand the discrete ***end points*** of the mechanisms of neurotransmission and regulation of bodily functions. If we are to supplement this complex chemistry machine, we must try and duplicate the entire path to the end result. We are not arrogant enough to claim that we (or the medical community) understand this complex path to the end reaction. Our approach therefore is to use the "natural PATH", (not just isolated natural components) to supplement the role of the amino acids in regulating the complex electrochemical machine we call the human body. How do we achieve this?

Simple: Nature puts the most potent and balanced combination of not only amino acids in short peptide chain form, but also other known (and unknown) factors such as Fibroblast Growth Factor in blastodermal to protoembryonic fluids preceding the formation of the crucial organs and embryo. We believe amino acids (in the form of di and tripeptides) derived from such fluids combined with the growth factors are able to enhance brain function because they are "precisely" engineered to support the most complex stage of birth of a living creature, the beginning; just like the take off is the

most complex function in flying an airplane, or the foundation and construction is the most complex function in the life of a building.

The health benefits of the hen egg have been known for centuries. Recently, further investigation of the mechanism of the development of an embryo in an egg during incubation revealed the scientific equivalent of the “miracle of life”. In earlier studies, whilst monitoring weight gain of the embryo during the incubation period, scientists (1) found very little gain in the first 9-10 days (7.5%), and then a sharp increase (1190% by end of incubation), suggesting rapid development of a body. The potency of the nutrients available to the embryo at this stage has always been assumed to be high, but it was only recently that the chemical structure of the original egg solids for these critical stages, termed blastodermal to protoembryoinic stages was obtained. During the blastodermal to protoembryonic stages of embryogenesis, oligopeptides with molecular weights from 0.5 to 1.0 kD were identified. Oligopeptides are compounds, which have 2 to 20 amino acids joined by a peptide bond. These short chains of amino acids are able to cross the digestive barrier without breaking down or changing the ratios and proportions (5). Peptides are far more potent than other neurotransmitters, requiring only small amounts to produce a profound effect.

Additionally, the uptake of the Fibroblast Growth Factor (FGF) (present in the protoembryonic fluid) by the embryo sharply increases between days 11 & 12. These embryonic peptides and the FGF have been isolated through a patented process (US Patent 5,641,517) precisely at the right stage of incubation, extracted and freeze dried to bring the “miracle of life” benefits to humans. The extract is termed Blastodermal & Protoembryonic stage Extract (BPE).

Extracting the protoembryonic fluid before the peptides and FGF are “used up” to build organs and bones, allows us to provide this building, repairing, maintenance mechanism of perfectly balanced amino acids, peptides and growth factors to humans.

But is a balanced peptide combination sufficient to show such drastic effects as described in testimonials from Laminine users? Nature has devised an extremely versatile mechanism to provide nutrition with miraculous precision to the embryo of living creatures. The precise blend of oligopeptides may be seen as building blocks, without a bridge, or a director. The role of such a director is fulfilled by a growth factor known as the Fibroblast Growth Factor, or FGF. FGF is prolific in protoembryonic liquid as well as the human placenta. On the 11^{th} day of the incubation cycle of a chicken egg, the embryonic tissue shows a steep increase in the FGF, with the appropriate peptides to form the solid organs and bones (A1). A detailed day-by-day study was performed in 1988 (A4, A11). Discovered only in the seventies, and also a peptide, this growth factor is critical in the development of embryos, including humans. However, it is not found to be circulating in the human adult bodies.

FGF is responsible for building the linings in the blood vessels, creating the infrastructure for the nutrients to flow to critical areas of the brain and organs. Research credits FGF with the potential to directly affect many neuro disorders because of clear results of the ability of FGF to affect the growth of neurites (A2). Neurites are signal senders (Axons) and signal receivers (dendrites) attached to the brain neurons.

Research (A7) has also shown clearly that new cell cultures show a dramatic increase in peptide and amino acid uptake in the presence of FGF. This result gives credence to the hypothesis that embryonic growth is influenced by a very precise mechanism, which combines unique combinations of amino acids, peptides and FGF.

Since FGF is not circulating in adults, multiple research projects on the effects of FGF serums to cure neuro disorders have been carried out.

Fundamental to the research is the fact discovered by Altman, J. in 1962 (A26) that multipotent neural STEM cells are formed by the body in response to abnormalities, and are resident in the Subventricular, subepyndymal and hippocampal subgranular zones. The brain is therefore ready to repair the damage, and these cells have shown to differentiate into a wide range of neurons (A27). Neurons derived from such neural stem cells are capable of migrating to various regions of the Central Nervous System. Over a decade of work, both in vivo and ex vivo has revealed that exposure to such neural stem cells to growth factors such as FGF permits direct differentiation along either neuronal or astrocytic lineages (A14, A25).

The discovery that STEM cells, both differentiated as well as undifferentiated in adult brains as well as organs can be nourished if the growth factor were present with the correct balance of peptides and amino acids, becomes the heart of the Laminine story. At Pendura, we have had faith that the natural serum contained in BPE MUST have all the factors (known and unknown) needed for embryo nourishment, because millions of years of flawless reproduction is proof. However, we also feel it is important for us to understand (to the best of “human” abilities) the “known” mechanisms and explain them to our customers. Our explanation should make it clear that simulating nature is not an easy task, and though the natural route to neuro nutrition is more expensive, we prefer that route to the approach our competitors take of formulating the “known” components.

The BPE in Laminine provides a natural, evolved base of low molecular weight oligopeptides of precise proportions with rapid transport through the digestive tract and neurotransmitter functions. Along with the peptides, the Fibroblast growth factor is also extracted at an optimum time, giving an extremely potent combination of nourishment to the existing stem cells in the adult body, as if the placenta was made available to them in adulthood.

Having found the mechanism and dominating factors, Pendura looked at the compatibility of modern day stress with embryonic nourishment. Modern life puts pressures on our mental health which evolution has not caught up with. Laminine takes the extraordinary blend of benefits from BPE and complements the amino acids with a precise formulation of balancing and enhancing peptides to "turbo charge" the effects from BPE related to brain activity. Having nature provide us with the mechanisms to transport and direct the amino acids, peptides and FGF required to deal with the modern life, Laminine provides benefits like no other nutritional supplement.

Adding specific, targeted vegetable protein ingredients: Vegetable protein, specifically certain legume proteins, have an essential amino acid profile, which is very close to that of the ideal protein for human nutrition (FAO/WHO 1985 and 2002). For Laminine, a patented process further isolates such a protein to eliminate the compounds, which neutralize the benefits of the essential amino acids. The result is an ingredient, which is high in Glutamic acid, (further enhancing the cognitive function of the brain), branched chain amino acids (to counter insomnia), Lysine (to control release of serotonin, controlling moods) and Arginine (promoting NO and growth hormone formation). The specially isolated protein therefore adds a synergistically potent composition to enhance brain activity.

Adding Marine: The high levels of Glycine in the specially extracted marine protein, combined with a significant amount of hydroxyproline to stabilize the glycine, makes it a primary candidate for brain food. By itself, Glycine is a neurotransmitter, primarily utilized by the brain to control glutamate levels. As a combination with BPE, it becomes a powerful force to enhance memory function in the brain.

Based on the testimonials received by consumers of Laminine and placebo studies done on individual components of Laminine, we were inspired to investigate the mechanisms that affect the positive results reported, especially the neurological effects. We found multitude of studies, which point to either the amino acids/peptides or FGF as isolated causes of similar, but less significant results. Unfortunately, in our opinion, the two different paths of research have not connected the relevance of the two components working in harmony and cohesion. At Pendura, we believe working together, these nutrients produce far more potent results, and our customers' testimonials are proof.

We therefore present the research on these ingredients in a bifurcated manner, combined with proof that cell cultures have a sharp increase in uptake of amino acids and peptides (A7), it should be obvious that the optimal way to nourish one's brain functions is by a combination of FGF and oligopeptides.

Increased workout ability due to rapid healing of stressed (wounded) muscle. Di-peptide Carnosine (a peptide containing amino acids alanine and histidine) has been found to

improve healing of wounds (1). Unhealed wounds are a constant source of inflammatory mediators and a substrate for infection. As such, they prolong the recovery of injured patients and may lead to multiple organ failure and death. It is believed that oligopeptides generated from dietary intake play a role in optimizing growth and healing. These peptides may directly stimulate cells involved in the growing or healing process or may act directly by augmenting the production of growth factors. Indeed FGF2 has been shown to heal wounded tissue and organs effectively. FGF2 is produced by the body in response to an external injury, to provide nutrition to the new stem cells for repair. (A28, A13).

In a 1997 study, immediately following surgery, (animal) subjects were randomized to receive either an amino acid diet or a peptide diet for 10 days and the strength of the wound was measured. Wound bursting pressure was found to be significantly higher in subjects receiving the peptide diets than in those just receiving amino acid diets. The authors suggest that dietary peptides may stimulate the production of growth factors such as growth hormone, insulin, or insulin growth factor (IGF-1). They also postulate that it is possible that the amino acid entry into the cell via peptide transporters is more efficient for stimulation of protein synthesis than entry in the form of just amino acids. Other possible mechanisms suggested by the authors for the increased wound healing with peptide versus non peptide diets include stimulation of collagen synthesis, increased blood flow to the wound, free radical scavenging, and generation of cytokine profiles which better support wound healing.

Stress, weight gain and Cortisol: The body releases cortisol when under stress. Cortisol raises the sugar level in the blood, increases blood pressure and performs a myriad of functions to help maintain balance. Unfortunately, evolution has not caught up with undue stress such as traffic jams, mean bosses, etc. and the cortisol released during such situations contributes to weight gain, blood pressure irregularities and hypertension. One of the mechanisms identified with the embryonic peptides contained in Laminine works via elevation of 17-ketosteroid levels in the adrenal glands, which improve anabolism through increased synthesis of androgens and a decrease in (the catabolic hormone) cortisol, which offer multiple health benefits (2). The elevation could be the result of a synergistic effect of the peptides with FGF2, as explained in a 1977 paper (A32), in which FGF2 is described as working in cohesion with ACTH (main source or signal for cortisol production) to regulate cell production and inhibition.

Dementia/Alzheimer's and other neurodisorder symptoms; In a 1994 study (2), the pulvinar nuclei of nine patients with histologically confirmed Alzheimer's disease and twelve young (9-28 years of age) and age matched controls (without dementia and with non-Alzheimer's dementia) were examined using a battery of histopathalogical methods. All patients with Alzheimer's disease had numerous lesions, while control patients with and without dementia had very few Alzheimer's lesions. If some of these lesions as well as many impaired organs and lesions within the brain could partially be

considered wounds, they may be able to benefit benefit from the rapid healing by carnosine explained above.

A compelling argument has been made to use FGF as a treatment for Huntington's Disease and other degenerative neural diseases (A23). In 2005, the Johns Hopkins University School of Medicine conducted a study in which they used FGF2 as a neurogenesis factor, and found that the FGF increased proliferation of the stem cells by 5 times. We believe results could be even better if the right blend of amino acids and peptides were also available to the stem cells as nutrition when the FGF connects with the stem cells. Other studies have focused on the use of FGF for regulation of the Central Nervous System neurogenesis. A 2005 paper (A24) from University of Louisville, reviews what we consider to be Pendura's view. The review focuses on the emerging view among the medical community that localized and overlapping pathways of growth factors, metalloproteases, neurotransmitters, and hormones regulate different aspects of neurogenesis within the neurogenic niches. They suggest further elucidation of crucial molecular regulators and integration of their signaling cascades should lead to more rational and effective approaches to harness the adult CNS neurogenesis.

The story is similar for other neuro disorders:
Regarding autism, schizophrenia and OCD.

Flora M. Vaccarino, M.D., at the Yale School of Medicine, writes concerning Fibroblast Growth Factor 2:
"The cerebral cortex controls higher cognitive functions. Connections between the cortex and basal ganglia control motor and cognitive programs, whereas connections between the cortex and the medial temporal region and amygdala mediate emotional behavior. Abnormalities in the development of the cerebral cortex and associated structures have been suggested to occur in several neuropsychiatric disorders, including schizophrenia, autism and obsessive compulsive disorder.
The human cortex is about 1000-fold greater than that of the mouse. This increase is largely due to an increase in surface area. Cortical surface area may be correlated with a higher capacity to perform increasingly complex cognitive operations.
Cerebral cortical neurons are generated during embryogenesis by the proliferation of cells situated around the lateral ventricles. Three factors can potentially influence the total number of cells generated and thus the final size of the cerebral cortex. These are the number of cortical progenitor cells present before neurogenesis starts (the founder cell population), the number of proliferative cycles these cells undergo before differentiating, and the amount of cell death.
Fibroblast growth factor 2 (FGF2), is a potent mitogen for cortical progenitor cells in vitro, particularly for the precursors of glutamatergic neurons (Vaccarino et al, Cerebral Cortex, 1995). The microinjection of FGF2 in the cerebral ventricles of rat embryos increases the proliferation of cortical progenitors in vivo, resulting in a dramatic expansion of cerebral cortical volume, total cell number and surface area (Vaccarino et al, Neuroscience Abstracts, 1995). FGF2 expands the size of the cortex by over 50%,

without altering its morphological features. These findings are of great interest from a developmental and evolutionary perspective and hold therapeutic promise as well, since FGF2 is one of the factors that is capable of maintaining the proliferation of stem cells in the adult mammalian brain.

Recovering from Stroke; Carnosine has recently been the focus of attention as a potential therapeutic agent for strokes have emerged from the demonstration of it's neuro-protective capabilities. In a 2008 paper investigating (3) the role of carnosine as a potential therapeutic agent for stroke from demonstration of it's neuroprotective capabilities, cites a 2007 study (12) in which carnosine treatment reduced the infarct volume (infarct volume is a common index for assessing the extent of brain injury) by 42.5% compared to treatment with other peptides. The authors state that their HPLC data suggests that exogenously administered carnosine results in increased cerebral levels. They prove that in response to a pMCAO (occlusion of the middle cerebral artery) carnosine immunoreactivity is enhanced in the brain.

In a separate study (A28), FGF2 was tested as a potent neurotrophic and angiogenic peptide. The rats with the FGF treatment showed decrease in infarct volume by 44%. FGF2 has also been shown by a study in 2005 (A23) to "block" cell death induced by mutant genes. This strongly suggests that FGF2 with the proper nutrients to back it up, first blocks further degeneration, and then proceeds to heal neural tissue.

FGF has also been shown to reduce toxicity in the neuron striatal cultures (A25).

Improved Vision: Depletion of glutathione has been proven to cause an uncoupling effect on retinal horizontal cells through oxidative stress. Glutathione is a tripeptide thiol compound and is a substrate for scavenging reactive oxygen radicals or toxins through the enzymes glutathione peroxidase and glutathione reductase (4).

In a 1999 study, Z.Y. ZHOU et al measured the retinal effects of glutathione depletion in Carp by partially depleting it with a glutathione inhibitor, L-buthionine sulfoximine (BSO). They measured the glutathione immediately after electrophysiological experiments in each preparation. The glutathione was allowed to recover over 4-7 days. During this period, H1 cell response to red light was measured. The response measuring technique showed that 4 days after the injection of BSO, the response was much higher. It is postulated that glutathione serves as a physiological reductant to protect critical sulfhydryl groups from oxidation by hydrogen peroxide and other oxidants (13).

Motivation/Depression: A double blind study has proven the powerful Glycine activity to elevate 17-ketosteroid levels in the adrenal glands, which improve anabolism through increased synthesis of androgens and a decrease in the catabolic hormone cortisol (6).

Patients with mild to moderate mood disorders according to Hamilton ratingscale (Ham-

D) and Beck Depression Inventory (BDI) were included in the study according to the protocol. The patients were randomly assigned to receive placebo, Deprevent™ or Deprevent™ Forte (commercial products with BPE) for 12 weeks. The main outcome was change in the Ham-D total score from baseline to 12 weeks as well change in BDI from baseline to controls after 3, 6 and 12 weeks.

57 patients concluded the study. There was a significant effect in favor of the two active groups in the primary outcome measures as compared to placebo. Between the two active groups, however, it was no significant difference in the outcome measures, even if it was a weak tendency in favor of the Deprevent™ Forte group. It was no reports of adverse effects in any of the groups during the study.

Other studies have shown certain oligopeptides modify temporarily the inborn properties of the hypothalamic motivation centers (7,8).

In a 2006 study, several universities collaborated to publish a paper, which showed lack of FGF2 as a major factor in depressed individuals brains.

Blood Pressure Regulation: In her Doctoral Thesis, Tina Jauhianen showed Tripeptides IPP (isoleucyl-prolyl-proline) and VPP (valyl-prolyl-proline) reduce hypertension (11) by inhibiting Angiotensin Converting Enzyme (ACE). ACE converts the body's Angiotensin I to Angiotensin II, which contracts blood vessels, resulting in high blood pressure. #
#
The clearest result regarding the effect on blood pressure was achieved in 24-hour ambulatory blood pressure measurement; the difference between the group that received peptides and the placebo group in lowering systolic and diastolic blood pressure was statistically significant. The 24-hour ambulatory measurement method is considered the most reliable.#
#
A 1998 study done in Germany showed that lack of FGF2 impaired cerebral cortex development, subsequently affecting the ability of the subject mice brains to regulate their blood pressure.#
#
Reduction in Arthritic Pain, Joint pain: In the late eighties and nineties, several studies (A33, A34, A35) have proven that FGF2 plays a major role in the process of balancing the synovial fluid (joint fluid) and growth of new bone cells through different pathways. Bone growth was observed on implants, as well as natural bones. #
#
Summary:#
#
We have outlined plausible explanations above for the benefits experienced by consumers of Laminine. As we move forward with this amazing product, we are certain there will be other testimonials with other benefits and will investigate the possible mechanisms for such benefits. An analysis of the Laminine formulation gives us an

insight into the amino acids present. Tests also confirm these amino acids are present mostly as oligopeptides. FGF2 has been confirmed in chick embryos by many studies after day 11, and in the protoembryonic liquid (A1, A3, A4, A9, A10, A11). If the peptides and growth factors are available for the maintenance, repair or building of the neuro system, there should be sufficient reason to believe it has far more outreaching effects than what we have experienced so far. We feel this is just the beginning of our investigations.

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