Tryptophan, serotonin, and aging

From the original article in 2006. Author: Ray Peat.

Beginning with the industrial production of glutamic acid (sold as MSG, monosodium glutamate), the public has been systematically misinformed about the effects of amino acids in the diet. The FDA has been industry's powerful ally in misleading the public. Despite research that clearly showed that adults assimilate whole proteins more effectively than free amino acids, much of the public has been led to believe that "predigested" hydrolized protein and manufactured free amino acids are more easily assimilated than real proteins, and that they are not toxic. Even if free amino acids could be produced industrially without introducing toxins and allergens, they wouldn't be appropriate for nutritional use.

Although some research shows that babies up to the age of 18 months can assimilate free amino acids, a baby formula containing hydrolyzed protein was associated with decreased serum albumin, which suggests that it interfered with protein synthesis.

The myth that free amino acids are "natural nutritional substances" has been used to promote the use of many products besides MSG, including aspartame, chelated minerals, and tryptophan.

Although several amino acids can be acutely or chronically toxic, even lethal, when too much is eaten, tryptophan is the only amino acid that is also carcinogenic. (It can also produce a variety of toxic metabolites, and it is very susceptible to damage by radiation.) Since tryptophan is the precursor of serotonin, the amount of tryptophan in the diet can have important effects on the way the organism responds to stress, and the way it develops, adapts, and ages.

When an inflammatory disease (eosinophilia-myalgia syndrome) was noticed in people using tryptophan tablets (1989-90), there was an intense campaign to exonerate the tryptophan itself by blaming the reaction on an impurity in one company's product. But the syndrome didn't occur only in the people who used that company's product, and similar changes can be produced by a high-tryptophan diet (Gross, et al., 1999).

There are people who advocate the use of tryptophan supplementation or other means to increase serotonin in the tissues as a treatment for the fibromyalgia syndrome, but the evidence increasingly suggests that excessive serotonin, interfering with muscle mitochondria, is a major factor in the development of that syndrome.

In 1965, Hans Selye showed that the injection of serotonin caused muscular dystrophy. Subsequent studies suggest that serotonin excess is involved in both muscular and nervous dystrophy or degeneration. (O'Steen, 1967; Narukami, et al., 1991; Hanna and Peat, 1989.)

The fatigue produced by "over-training" is probably produced by a tryptophan and serotonin overload, resulting from catabolism of muscle proteins and stress-induced increases in serotonin. Muscle catabolism also releases a large amount of cysteine, and cysteine, methionine, and tryptophan suppress thyroid function (Carvalho, et al., 2000). Stress also liberates free fatty acids from storage, and these fatty acids increase the uptake of tryptophan into the brain, increasing the formation of serotonin. Since serotonin increases ACTH and cortisol secretion, the catabolic state tends to be self-perpetuating. This process is probably a factor influencing the rate of aging, and contributing to the physiological peculiarities of aging and depression.

Malnutrition, and specifically protein deficiency, produces an inflammatory state that involves extreme serotonin dominance. Stress or malnutrition prenatally or in infancy leads to extreme serotonin dominance in adulthood. Other functions of tryptophan are reduced, as more of it is turned into serotonin.

Decreasing tryptophan or decreasing serotonin improves learning and alertness, while increased serotonin impairs learning.

Tryptophan is an essential amino acid for reproduction and growth of the young animal. Most research on the nutritional requirements for amino acids has been done on farm animals, because of the economic incentive to find the cheapest way to produce the fastest growth. Farmers aren't interested in the nutritional factors that would produce the longest-lived pigs. Some research has been done on the amino acid requirements of rats over a significant part of their short lifespans. In rats and farm animals, the amount of tryptophan required decreases with time as the rate of growth slows.

In some ways, rats never really mature, since they keep growing for nearly their whole lifespan. Their growth stops just a short time before they die, which is usually around the age of two or three years. (At this age, rats' cells still retain approximately the same high water content seen in the cells of a two year-old child.) They usually become infertile about half-way through their lifespan. If we try to draw conclusions about amino acid requirements from the rat studies, I think we would want to extrapolate the curve for the decreasing need for tryptophan, far beyond the point seen during the rat's short life. And those "requirements" were determined according to the amounts that produced a maximum rate of growth, using the index of the pig farmers, as if the rats were being studied for possible use as meat.

When rats were fed a diet completely lacking tryptophan for a short period, or a diet containing only one fourth of the "normal" amount for a more prolonged period, the results were surprising**:** They kept the ability to reproduce up to the age of 36 months (versus 17 months for the rats on the usual diet), and both their average longevity and their maximum longevity increased significantly. They looked and acted like younger rats. (A methionine-poor diet also has dramatic longevity-increasing effects.)

On the tryptophan-poor diet, the amount of serotonin in the brain decreased. When brain serotonin decreases, the level of testosterone in male animals increases. More than 20 years ago, a chemical (p-chlorophenylalanine) that inhibits serotonin

synthesis was found to tremendously increase libido.

In old age, the amount of serotonin in the brain increases. This undoubtedly is closely related to the relative inability to turn off cortisol production that is characteristic of old age (Sapolsky and Donnelly, 1985). Hypothyroidism increases the formation of serotonin, as does cortisol (Henley, et al., 1997, 1998; Neckers and Sze, 1976).

In white hair, the amount of tryptophan is higher than in hair of any other color. Although serotonin and tryptophan are very important during rapid growth, their presence in senile tissues is probably closely associated with the processes of decline. The hair loss that occurs in hypothyroidism, postpartum syndrome, and with the use of drugs such as St. John's wort (which can also cause the "serotonin syndrome") could be another effect of excess serotonin.

Serotonin stimulates cell division and tends to increase the formation of connective tissue, so its formation should be closely regulated once full growth is achieved. It contributes to the age- or stress-related thickening of blood vessels, and other fibrotic processes that impair organ function.

The metabolic rate (eating more without gaining extra weight) and ability to regulate body temperature are increased by early tryptophan deprivation. (Ashley and Curzon, 1981; Segall and Timiras, 1975.) The ability to oxidize sugar is impaired by serotonin, and several drugs with antiserotonin actions are being used to treat diabetes and its complications, such as hypertension, obesity, and foot ulcers.

An excess of tryptophan early in life, stress, or malnutrition, activates the system for converting tryptophan into serotonin, and that tendency persists into adulthood, modifying pituitary function, and increasing the incidence of pituitary and other cancers.

Serotonin's contribution to high blood pressure is well established. It activates the adrenal cortex both directly and through activation of the pituitary. It stimulates the production of both cortisol and aldosterone. It also activates aldosterone secretion by way of the renin-angiotensin system. Angiotensin is an important promoter of inflammation, and contributes to the degeneration of blood vessels with aging and stress. **It can also promote estrogen production.**

In the traditional diet, rather than just eating muscle meats, all the animal parts were used. Since collagen makes up about 50% of the protein in an animal, and is free of tryptophan, this means that people were getting about half as much tryptophan in proportion to other amino acids when they used foods such as "head cheese," ox-tails, and chicken feet.

While some of the toxic effects of an excess of individual amino acids have been investigated, and some of the protective or harmful interactions resulting from changing the ratios of the amino acids have been observed, the fact that there are about 20 amino acids in our normal diet means that there is an enormous number of possibilities for harmful or beneficial interactions.

The optimal quantity of protein in the diet has traditionally been treated as if it were a matter that could be resolved just by observing the rate of growth when a certain protein is given in certain quantities, along with "standard amounts" of calories and other nutrients. This kind of research has been useful to farmers who want to find the cheapest foods that will produce the biggest animals in the shortest time. But that kind of research climate has spread a degraded concept of nutrition into the culture at large, influencing medical ideas of nutrition, the attitudes of consumers, and the policies of governmental regulatory agencies.

When synthetic amino acids are used to supplement natural proteins, they are usually chosen according to irrelevant models of the "ideal protein's" composition, and many toxic contaminants are invariably present in the synthetic free amino acids.

For the present, the important thing is to avoid the use of the least appropriate food products, while choosing natural foods that have historical, epidemiological, and biochemical justification.

Whey has been promoted as a protein supplement, but it contains a slightly higher proportion of tryptophan than milk does. Cheese (milk with the whey removed) contains less tryptophan. Some people have been encouraged to eat only the whites of eggs, "to avoid cholesterol," but the egg albumin is rich in tryptophan.

The expensive tender cuts of meat contain excessive amounts of cysteine and tryptophan, but bone broth (gelatin) and the tougher cuts of meat contain more gelatin, which lacks those amino acids. Many fruits are deficient in tryptophan, yet have very significant quantities of the other amino acids. They also contain some of the "carbon skeleton" (keto-acid) equivalents of the essential amino acids, which can be converted to protein in the body.

Serotonin excess produces a broad range of harmful effects**:** Cancer, inflammation, fibrosis, neurological damage, shock, bronchoconstriction, and hypertension, for example. Increased serotonin impairs learning, serotonin antagonists improve it.

The simplest, nonessential, amino acid, glycine, has been found to protect against carcinogenesis, inflammation, fibrosis, neurological damage, shock, asthma, and hypertension. Increased glycine improves learning (Handlemann, et al., 1989; File, et al., 1999), glycine antagonists usually impair it. Its antitoxic and cytoprotective actions are remarkable. Collagen, besides being free of tryptophan, contains a large amount of glycine--32% of its amino acid units, 22% of its weight.

The varied antiinflammatory and protective effects of glycine can be thought of as an antiserotonin action. For example, serotonin increases the formation of TNF (tumor necrosis factor, also called cachectin), glycine inhibits it. In some situations, glycine is known to suppress the formation of serotonin. **Antagonists of serotonin can potentiate glycine's effects** (Chesnoy-Marchais, et al., 2000). People who ate traditional diets, besides getting a lower concentration of tryptophan, were getting a large amount of glycine in their gelatin-rich diet.

Gelatin, besides being a good source of glycine, also contains a large amount of proline, which has some antiexcitatory properties similar to glycine.

If a half-pound of steak is eaten, it would probably be reasonable to have about 20 grams of gelatin at approximately the same time. Even a higher ratio of gelatin to muscle meat might be preferable.

Carbon dioxide, high altitude, thyroid, progesterone, caffeine, aspirin, and decreased tryptophan consumption protect against excessive serotonin release. When sodium intake is restricted, there is a sharp increase in serotonin secretion. This accounts for some of the antiinflammatory and diuretic effects of increased sodium consumption--increasing sodium lowers both serotonin and adrenalin.

The polyunsaturated oils interact closely with serotonin and tryptophan, and the short and medium chain saturated fatty acids have antihistamine and antiserotonin actions. Serotonin liberates free fatty acids from the tissues, especially the polyunsaturated fats, and these in turn liberate serotonin from cells such as the platelets, and liberate tryptophan from serum albumin, increasing its uptake and the formation of serotonin in the brain. Saturated fats don't liberate serotonin, and some of them, such as capric acid found in coconut oil, relax blood vessels, while linoleic acid constricts blood vessels and promotes hypertension. Stress, exercise, and darkness, increase the release of free fatty acids, and so promote the liberation of tryptophan and formation of serotonin. Increased serum linoleic acid is specifically associated with serotonin-dependent disorders such as migraine.

Coconut oil, because of its saturated fatty acids of varied chain length, and its low linoleic acid content, should be considered as part of a protective diet.

In the collagen theory of aging, it is argued that changes in the extracellular matrix are responsible for isolating cells from their environment, reducing the availability of nutrients and oxygen, and reducing their ability to send and receive the chemical signals that are needed for correct adaptive functioning.

In diabetes, basement membranes are thickened, and in a given volume of tissue there are fewer capillaries. This effect probably involves excessive serotonin (Kasho, et al., 1998). Old animals contain a higher proportion of collagen. Old tendons (or tendons that have been exposed to excessive estrogen, which stimulates the formation of collagen) are more rigid, and behave almost as if they have been partly cooked. In diseases such as carcinoid, in which very large amounts of serotonin are released systemically, fibrosis is exaggerated, and may be the direct cause of death. Radiation and oxygen deprivation also lead to increased tissue fibrosis.

In specific fibrotic conditions, such as cirrhosis of the liver, it is known that glycine and saturated fats can reverse the fibrosis. In fibrosis of the heart, thyroid hormone is sometimes able to reverse the condition.

I think these facts imply that excessive tryptophan, estrogen, and polyunsaturated fats contribute significantly, maybe decisively, to the degenerative changes that occur in aging. Experiments have separately shown that reducing dietary tryptophan or unsaturated fats can extend the healthy lifespan, and several antiestrogenic interventions (removal of the pituitary, or supplementing with progesterone) can slow age-related changes and delay degenerative diseases. Since these factors interact, each tending to promote the others, and also interact with exogenous toxins, excess iron accumulation, and other stressors, it would be reasonable to expect greater results when several of the problems are corrected at the same time.

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Clin Exp Neurol 1978;15:190-6. **Individual free fatty acids and migraine.** Anthony M Total plasma free fatty acids (FFAs), platelet serotonin content and plasma stearic, palmitic, oleic and linoleic acids were estimated in 10 migrainous patients before, during and after a migraine attack. Total and individual plasma FFA levels rose and platelet serotonin fell in most patients. Comparison of the pre-headache and headache mean values showed that of the FFAs linoleic acid rises most during headache. **10 non-migrainous controls had platelet serotonin content estimated before and after the ingestion of 20g linoleic acid. All showed a significant fall in platelet serotonin in the post-ingestion period. It is shown that linoleic acid releases platelet serotonin in vitro, and this study suggests that it has the same action in vivo.** Further, it is the precursor of all prostaglandins in the body and its marked elevation during migraine may serve as a source of increased prostaglandin E1 (PGE1) synthesis. It is **suggested that linoleic acid plays an important role in the biochemical process of the migraine attack, acting both as a serotonin releasing factor and a source** of PGF1, the vasodilating action of which can aggravate the clinical symptoms of migraine.

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J Clin Psychopharmacol 1999 Dec;19(6):506-12. **Beneficial effects of glycine (bioglycin) on memory and attention in young and middle-aged adults.** File SE, Fluck E, Fernandes C. ."The effects of Bioglycin(Konapharma, Pratteln, Switzerland), a biologically active form of the amino acid glycine, were . . . studied in healthy students (mean age, 20.7 years) and middle-aged men (mean age, 58.9 years) with tests that measured attention, memory and mood, using a double-blind, randomized, crossover design. Compared with the young group, the middle-aged group had significantly poorer verbal episodic memory, focused, divided, and sustained attention; they also differed in their subjective responses at the end of testing. Bioglycin significantly improved retrieval from episodic memory in both the young and the middle-aged groups, but it did not affect focused or divided attention. However, the middle-aged men significantly benefited from Bioglycin in the sustained-attention task. The effects of Bioglycin differed from those of other cognitive enhancers in that it was without stimulant properties or significant effects on mood, and it primarily improved memory rather than attention. It is likely to be of benefit in young or older people in situations where high retrieval of information is needed or when performance is impaired by jet lag, shift work, or disrupted sleep. It may also benefit the impaired retrieval shown in patients with schizophrenia, Parkinson's disease, and Huntington's disease.

Brain Res 1997 Sep 12;768(1-2):43-8. **Mobilization of arachidonate and docosahexaenoate by stimulation of the 5-HT2A receptor in rat C6 glioma cells.** Garcia MC, Kim HY Laboratory of Membrane Biochemistry and Biophysics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD 20852, USA. **"In this study, we demonstrate that astroglial 5-HT2A receptors are linked to the mobilization of polyunsaturated fatty acids (PUFA). Stimulation of C6 glioma** cells, prelabeled with [3H]arachidonate (AA, 20:4n6) and [14C]docosahexaenoate (DHA, 22:6n3), with serotonin and the 5-HT(2A/2C) receptor agonist (+/-)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI) resulted in the mobilization of both [3H] and [14C] into the supernatant of the cell monolayers. The increased radioactivity in the supernatant was mainly associated with free fatty acids." "These results indicate that the 5-HT2A receptor is coupled to the mobilization of PUFA."

Neurosci Lett 1995 May 5;190(2):143-5. **Serotonin involvement in the spontaneous alternation ability: a behavioral study in tryptophan-restricted rats.** Gonzalez-Burgos I, Olvera-Cortes E, Del Angel-Meza AR, Feria-Velasco A. Laboratorio de Psicobiologia, Centro de Investigacion Biomedica de Occidente, IMSS, Guadalajara, Jal., Mexico. Spontaneous alternation (SA) is controlled by septal cholinergic terminals in the hippocampus. Serotoninergic terminals end on cholinergic nerve endings in the hippocampus, and their possible role in SA was investigated in rats fed with a tryptophan-deficient diet, from weaning to 60 days of age. **A T-maze was used for the test. At the age**

of 40 days, an increase in SA occurred in the tryptophan deficient rats, although this effect disappeared by 60 days of age. A modulatory role of serotonin in the psychoneural control of SA is suggested, and it may be through presynaptic inhibition of hippocampal cholinergic terminals.

Physiol Behav 1998 Jan;63(2):165-9. **Effect of tryptophan restriction on short-term memory.** Gonzalez-Burgos I, Perez-Vega MI, Del Angel-Meza AR, Feria-Velasco A. Centro de Investigacion Biomedica de Michoacan, Instituto Mexicano del Seguro Social, Morelia. Several brain regions are involved in the learning process that is integrated from sensorial inputs. It is thereafter consolidated in short- (STM) or long-term memory. Serotonin is strongly related to both types of memory, and particularly, to STM, however, its regulatory role is still unclear. In this study, the effects of tryptophan (TRY) restriction on learning and STM were evaluated. Ten Sprague-Dawley female rats were fed with a TRY-restricted diet (0.15g/100g) starting from postnatal Day 21. At 21, 40, and 60 days of age, 5 trials per animal were carried out in a "hard-floor"-Biel maze, after 24 h of water abstinence. The number of errors per trial were registered before reaching the goal. **At both 40 and 60 days, experimental rats committed less errors than controls. Likewise, the TRY-restricted group learned the task from the second trial on, whereas controls did not solve it until the third trial.** TRY restriction, and therefore brain serotonin reduction, could impair normal cholinergic activity in some areas such as the hippocampus and the cerebral cortex, where involvement in learning and memory is well documented. Morphological and neurochemical plastic events could also be related to the more efficient performance of the task by the TRY-restricted rats.

Am J Physiol 1997 Jul;273(1 Pt 2):R324-30. **Mechanisms in the pressor effects of hepatic portal venous fatty acid infusion.** Grekin RJ, Dumont CJ, Vollmer AP, Watts SW, Webb RC Portal venous infusion of oleate solution has pressor effects. We have examined efferent mechanisms, measured the response to sustained infusion, and determined the effect of linoleate. Eight conscious animals received concurrent infusions of prazosin or vehicle with portal venous infusion of oleate. Oleate alone **increased mean arterial pressure from 109.0 +/- 4.1 to 123.0 +/- 5.8 mmHg (P = 0.02), whereas no increase in blood pressure occurred when oleate was infused** with prazosin. In 10 rats, concurrent infusion of losartan had no effect on the pressor activity of portal oleate infusion. Twenty-two animals received portal oleate or vehicle as a continuous infusion for 7 days. Mean arterial pressure (126.1 +/- 2.0 vs. 107.8 +/- 2.6 mmHg, P < 0.001) and heart rate (383 +/- 5 vs. 366 +/- 5, P = 0.0257) were increased in oleate-infused animals. No differences in plasma fatty acids, glucose, insulin, pressor hormones, liver enzymes, or in vitro arterial pressor responsiveness were observed. "Portal venous infusion of **linoleate increased arterial pressure by 12.2 +/- 3.2 mmHg (P = 0.033). These results indicate that alpha-adrenergic activity is necessary for the acute pressor effects of portal oleate, that sustained portal oleate infusion results in persistent blood pressure elevation, and that other long-chain fatty acids besides oleate have pressor effects."**

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Pain 1989 Aug;38(2):145-50. **Ketanserin in reflex sympathetic dystrophy. A double-blind placebo controlled cross-over trial.** Hanna MH, Peat SJ.

Synapse 1997 Sep;27(1):36-44. **Thyroid hormones and the treatment of depression: an examination of basic hormonal actions in the mature mammalian brain.** Henley WN, Koehnle TJ. "The lack of mechanistic insight reflects, in large part, **a longstanding bias that the mature mammalian central nervous system is not an important target site for thyroid hormones."**

Am J Physiol 1997 Feb;272(2 Pt 2):H894-903. **Hypothyroid-induced changes in autonomic control have a central serotonergic component.** Henley WN, Vladic F. Three experiments were conducted in unanesthetized rats made hypothyroid (Hypo) or maintained as euthyroid controls (Eu) to examine general cardiovascular responsiveness [experiment I (Exp I)]; responsiveness to a serotonin (5-HT2) agonist, dl-2,5-dimethoxy-4-iodoamphetamine [DOI intracerebroventricularly; experiment II (Exp II)]; or responsiveness to a 5-HT(1A) agonist dl-8-hydroxydipropyl-aminotetralin hydrobromide [8-OH-DPAT intracerebroventricularly; experiment III (Exp III)]. In Exp I, intravenous infusions of phenylephrine and nitroprusside provided little evidence that findings in Exp II and III were caused by generalized impairment in cardiovascular responsiveness in Hypo. In Exp II and III, Eu and Hypo were given either intra-arterial atropine or vehicle. Atropine significantly elevated heart rate (Exp II and III) and mean arterial pressure (Exp II) in Eu only. When compared with Eu, Hypo had a reduced pressor response (5.2 vs. 20.1%), an attenuated pulse pressure response (19.3 vs. 35.4%), and a more robust bradycardia (-17.7 vs. -7.0%) in response to DOI. These differences were atropine sensitive. In Exp III, Hypo had larger decrements in mean arterial pressure (-9.0 vs. -5.1%), heart rate (-13.9 vs. - 7.7%), and body temperature (-4.5 vs. -2.7%) in response to 8-OH-DPAT in comparison to Eu. Parasympathetic involvement in the differential responses to 8-OH-DPAT was less clear than with DOI. Deranged autonomic control in hypothyroidism may be caused, in part, by changes in central serotonergic activity.

Brain Res 1986 Mar;390(2):221-6. **Brain serotonin synthesis and Na+,K+-ATPase activity are increased postnatally after prenatal administration of L-tryptophan.** Hernandez-Rodriguez J, Chagoya G. The effect of prenatal L-tryptophan supplementation on the serotonin (5-HT) synthesis and the activity of Na+,K+-ATPase in the cerebral cortex was studied during postnatal development, from birth up to day 30. A parallel and **significant elevation of the serotonin content and the activity of tryptophan-5-hydroxylase was observed in the brain of infant rats born to mothers treated with L-tryptophan, as related to non-treated controls. The** activity of Na+,K+-ATPase was also significantly elevated at the different ages studied throughout the developmental period, as related to controls. These results suggest an important role of L-tryptophan in the early regulation of the **serotonin-synthesizing machinery, which lasts postnatally. Elevation of ATPase activity seems to be associated to the elevation in the activity of the 5-HT system.**

Brain Res 1977 Mar 4;123(1):137-45. **Daily variations of various parameters of serotonin metabolism in the rat brain. II. Circadian variations in serum and cerebral tryptophan levels: lack of correlation with 5-HT turnover.** Hery F, Chouvet G, Kan

JP, Pujol JF, Glowinski J "Significant circadian variations in 5-HT and 5-HIAA levels were found in cerebral tissues." "Important significant circadian variations in free and total serum tryptophan levels were also observed. In both cases, the maximal levels were found during the middle of the dark phase after the peak of 5-HIAA levels." "The diurnal changes in tryptophan content in cerebral tissues seemed thus related to those found in serum."

Kidney Int 1998 Oct;54(4):1083-92. **Serotonin enhances the production of type IV collagen by human mesangial cells.** Kasho M, Sakai M, Sasahara T, Anami Y, Matsumura T, Takemura T, Matsuda H, Kobori S, Shichiri M.

Pharmacol Biochem Behav 1977 Sep;7(3):245-52. **Fatty acid and tryptophan changes on disturbing groups of rats and caging them singly.** Knott PJ, Hutson PH, Curzon G The effects of disturbing groups of 24 hr fasted rats on plasma unesterified fatty acid (UFA) and tryptophan concentrations and brain tryptophan concentrations were investigated. Removing rats from cages rapidly increased plasma UFA and corticosterone and decreased plasma and whole blood tryptophan of cage mates. The disturbance also appeared to influence biochemical values of rats in other cages within the same chamber. Effects specific to individual cages were also suggested. In subsequent experiments 24 fasting rats caged together were rapidly transferred to 24 separate cages and killed at intervals. Plasma UFA rose to a maximum by 12 min and then fell toward initial values. Plasma total tryptophan concurrently fell then rose. Its percentage in the free (ultrafilterable) state, and in some experiments the absolute values of free tryptophan rose then fell. When the latter rise was marked **then brain tryptophan and the 5-HT metabolite 5-hydroxyindoleacetic acid rose.** Tyrosine changes were negligible. Thus altered brain tryptophan level and 5-HT metabolism may be associated with plasma tryptophan changes caused by brief environmental disturbance.

J Insect Physiol 2000 May 1;46(5):793-801. **Effect of an amino acid on feeding preferences and learning behavior in the honey bee, Apis mellifera.** Kim YS, Smith BH. **"Subjects preferred to feed on a sucrose stimulus that contained glycine, and the highest relative preference was recorded for the highest concentration of glycine." "All concentrations of glycine enhanced the rate and magnitude of a conditioned response to an odor . . . ."**

Eur J Pharmacol 1981 May 22;71(4):495-8. **Antagonism of L-glycine to seizures induced by L-kynurenine, quinolinic acid and strychnine in mice.** Lapin IP.

Int J Circumpolar Health 1998;57 Suppl 1:386-8. **Seasonal variation of the amino acid, L-tryptophan, in interior Alaska.** Levine ME, Duffy LK. "The seasonal pattern of L-tryptophan was studied in a Fairbanks, Alaska, population that was unadapted to the extreme light variations of the North. Previously, this population was shown to exhibit seasonal behavior effects such as increases in fatigue and sleep duration, as well as endocrine effects such as increases in melatonin levels and phase shifting." "Prominent results included finding increased levels in the winter at several different diurnal time points. These findings support hypotheses which relate underlying physiological adaptations to the North to the increased incidence of behavioral disorders such as depression and alcoholism."

Infect Immun 2001 Sep;69(9):5883-91. **Dietary glycine prevents peptidoglycan polysaccharide-induced reactive arthritis in the rat: role for glycine-gated chloride channel.** Li X, Bradford BU, Wheeler MD, Stimpson SA, Pink HM, Brodie TA, Schwab JH, Thurman RG.

J Neurol Sci 1989 Jan;89(1):27-35. **Polyamine biosynthetic decarboxylases in muscles of rats with different experimental myopathies.** Lorenzini EC, Colombo B, Ferioli ME, Scalabrino G, Canal N.

Int J Dev Neurosci 1996 Aug;14(5):641-8. **Nutritional recovery does not reverse the activation of brain serotonin synthesis in the ontogenetically malnourished rat.** Manjarrez GG, Magdaleno VM, Chagoya G, Hernandez J Coordinacion de Investigacion Biomedica del Centro Medico Nacional, I.M.S.S. Mexico, D.F. In the present work we confirm that gestational malnutrition effects body and brain composition and results in an activation of the synthesis of the brain neurotransmitter 5-hydroxytryptamine. These results also demonstrate more activity of the rate-limiting enzyme tryptophan hydroxylase in the malnourished fetal and postnatal brain. However, the activity of this enzyme remains increased in the brain of nutritionally recovered animals accompanied by an increase in the synthesis of 5-hydroxytryptamine. We therefore suggest that, in the nutritionally recovered animal, the mechanism of activation of this biosynthetic path in the brain may be not dependent on the increased **availability of free L-tryptophan observed in malnourished animals, but might be due to a specific change in the enzyme complex itself. This hypothesis is** supported by the fact that plasma free and brain L-tryptophan return to normal in the recovered animal.

Brain Res 1997 Nov 7;774(1-2):265-8. **Tryptophan ingestion by gestant mothers alters prolactin and luteinizing hormone release in the adult male offspring.** Martin L, Rodriguez Diaz M, Santana-Herrera C, Milena A, Santana C.

Rev Esp Fisiol 1984 Jun;40(2):213-9. **[Lipolytic effect of serotonin in vitro].** [Article in Spanish] Martinez-Conde A, Mayor de la Torre P, Tamarit-Torres J The lipolytic action of serotonin on isolated adipocytes from the adipose tissue of rats has been studied. The adipocytes were incubated in serotonin 10(-6) M. Changes both in concentration and composition of the free intra and extracellular fatty acids as well as diacylglycerides through liquid gas chromatography were evaluated at different intervals. A lower concentration of **free fatty acids and diacylglycerides is produced during the first minutes of incubation as well as a subsequent increase in the concentration of both, which becomes greatest after 20-30 minutes. The composition of both lipidic fractions** (FFA and DAG) into fatty acids at 5, 10, 20 and 30 minutes, is related to the composition of the triacylglycerides (TAG), since during the esterification **process a decline in the DAG of linoleic and palmitoleic acid is observed, both acids arranging themselves preferably in the TAG 2 position. Whereas the inverse process occurs during lipolysis; i.e. an increase in the proportion of the acids** in the 2 position. In the FFA fraction, a higher proportion of fatty acids, preferential by arranged in positions 1 + 3 of the TAG's is observed. Similarly a decrease is observed in the extracellular concentration of FFA in the presence of serotonin with respect to the controls, a fact which has been described by other authors. An analysis of the present data leads us to revise the possible **role of "Cahill's cycle" (simultaneous activation of the DAG-acyl-transferase and the HSL-TAG-lipase) in the action of serotonin and other hormones.**

Nahrung 1991;35(9):961-7. **[The effect of different protein diets on longevity and various biochemical parameters of aged rats].** Medovar BJa, Petzke KJ, Semesko TG, Albrecht V, Grigorov JuG Institut fur Gerontologie, AMW, UdSSR, Kiev. In this work 23 month old rats were fed for 200 days with different protein diets (NT-diet: 19% protein, 72% of animal origin and LP-diet: 8.8% protein exclusively of vegetable origin). Some metabolic parameters and lifespan (on the base of a 50% death-rate) were determined. The relations of the liver free amino **acids glycine + alanine and tyrosine + phenylalanine + branched chain amino acids and the ratio of phenylalanine/tyrosine were determined to be higher in the LP-group.** Phenylalanine in liver and urea concentrations in liver and serum were lower in the LP-group. Furthermore the dopamine or serotonin levels were significantly lower in lateral and medial or lateral regions of the hypothalamus respectively in LP-diet fed rats. The norepinephrine content was not modified by **the diets. The median lifespan of 23 month old rats was higher by 24% following LP-treatment. These results suggest that the protein component (amino acids) of** different diets may modify metabolic parameters and lifespan of animals by mechanisms in which the central regulation may be involved.

J Neurol Sci 1976 May;28(1):41-56. **Skeletal muscle necrosis following membrane-active drugs plus serotonin.** Meltzer HY.

Brain Res Bull 1977 Sep-Oct;2(5):347-53. **Effects of developmental protein malnutrition on tryptophan utilization in brain and peripheral tissues.** Miller M, Leahy JP, McConville F, Morgane PJ, Resnick O.

Exp Neurol 1977 Oct;57(1):142-57. **Tryptophan availability: relation to elevated brain serotonin in developmentally protein-malnourished rats.** Miller M, Leahy JP, Stern WC, Morgane PJ, Resnick O.

Synapse 1990;6(4):338-43. **Age-related changes of strychnine-insensitive glycine receptors in rat brain as studied by in vitro autoradiography**. Miyoshi R, Kito S, Doudou N, Nomoto T. "3H-glycine binding sites were most concentrated in the hippocampus, cerebral cortex, and olfactory tubercle, and moderate densities of binding sites were located in the striatum, nucleus accumbens, amygdala, and certain thalamic nuclei." **"In aged animals, severe decline of 3H-glycine binding sites was observed in the telencephalic regions including the hippocampus and cerebral cortex." "These results suggest that the decrease of glycine receptors in particular brain regions has some relation with changes of neuronal functions associated with aging process in these areas.**"

Enzyme 1976;21(6):481-7. **Inhibition of actomyosin ATPase by high concentrations of 5-hydroxytryptamine. Possible basis of lesion in 5HT-induced experimental myopathy.** Mothersill C, Heffron JJ, McLoughlin JV.

Brain Res 1975 Jul 25;93(1):123-32. **Regulation of 5-hydroxytryptamine metabolism in mouse brain by adrenal glucocorticoids.** Neckers L, Sze PY "A single injection of **hydrocortisone acetate (HCA; 20 mg/kg, i.p.) accelerated the accumulation of 5-HT in whole brain after inhibition of monoamine oxidase activity by paragyline. The hormone did not appear to change brain tryptophan hydroxylase or 5-hydroxytryptophan decarboxylase activity. However, tryptophan levels in brain were elevated by 50% within 1 h after treatment with HCA."**

Proc Soc Exp Biol Med 1967 Nov;126(2):579-83. **Serotonin antagonist increases longevity in mice with hereditary muscular dystrophy.** O'Steen WK.

Mech Ageing Dev 1988 Apr;43(1):79-98. **Histology and survival in age-delayed low-tryptophan-fed rats. Ooka H, Segall PE, Timiras PS.** Diets containing tryptophan in concentrations 30 and 40 percent of those fed to controls from weaning to 24-30 months or more, can delay aging in Long-Evans female rats. Mortality among low-tryptophan-fed rats was greater in the juvenile period, but substantially less than controls at late ages. Histological biomarkers of aging were also delayed after tryptophan restriction in some organs (liver, heart, uterus, ovary, adrenal and spleen) but not in others (kidney, lung, aorta). Brain serotonin levels were low in tryptophan-deficient rats but showed remarkable capacity for rehabilitation. Effects on early and late mortality and brain levels of serotonin were proportional to the severity of the restriction.

Age Ageing 1985 Mar;14(2):71-5. **Plasma tryptophan, age and depression.** Phipps DA, Powell C. Plasma, obtained from 131 nondepressed, otherwise healthy subjects aged from 17 to 102 years, and 22 depressed subjects aged over 70 years, was analysed for total and free tryptophan. Variation with age was found in total tryptophan. **This association has not been described hitherto. There was a significant increase in total tryptophan and a non-significant increase in free tryptophan with depression. This is in contrast to some studies in younger people showing a decline in plasma tryptophan in depressed subjects.**

Bratisl Lek Listy 1975 Jul;64(1):58-63. **[The effect of serotonin on the release of free fatty acids from human and rat adipose tissue (author's transl)].** [Article in Czech] Rath R, Kujalova V.

Adv Exp Med Biol 1999;467:497-505. **Oxidative damage in rat tissue following excessive L-tryptophan and atherogenic diets.** Ronen N, Livne E, Gross B.

FASEB J 1994 Dec;8(15):1302-7. **Methionine restriction increases blood glutathione and longevity in F344 rats.** Richie JP Jr, Leutzinger Y, Parthasarathy S, Malloy V, Orentreich N, Zimmerman JA "Met restriction resulted in a 42% increase in mean and 44% increase in maximum life span, and in 43% lower body weight compared to controls ($P < 0.001$). Increases in blood GSH levels of 81% and 164% were observed in mature and old Met-restricted animals, respectively ($P < 0.001$)."

Carcinogenesis 1999 Nov;20(11):2075-81. **Dietary glycine prevents the development of liver tumors caused by the peroxisome proliferator WY-14,643.** Rose ML, Cattley RC, Dunn C, Wong V, Li X, Thurman RG.

Mech Ageing Dev 1983 Nov-Dec; 23(3-4):245-52. **Low tryptophan diets delay reproductive aging.** Segall PE, Timiras PS, Walton JR. Newly weaned female rats fed diets severely deficient in the essential amino acid tryptophan show marked delays in reproductive aging, with conception and delivery occurring as late as 36 months. The rate of aging in these rats seems inversely related to both their early growth rates and the accessibility of brain tryptophan. The subsequent age retardation may depend on a reduction in both early cell loss and rate of brain maturation.

Mech Ageing Dev 1978 Jan;7(1):1-17. **Neural and endocrine development after chronic tryptophan deficiency in rats: I. Brain monoamine and pituitary responses.** Segall PE, Ooka H, Rose K, Timiras PS. "Caloric restriction and tryptophan deficient diets have been shown to delay aging in the immature laboratory rat." "Another group of animals, in which growth and maturation was delayed by feeding d,1-parachlorophenylalanine (PCPA) showed decreases in serotonin, norepinephrine and dopamine concentrations in all brain regions investigated. All treatments employed to arrest growth and maturation resulted in pituitary alterations manifested by gross, histological and ultrastructural changes. It is postulated that there maturation- and age-retarding treatments delay the development of the central nervous system resulting in postponed maturation of the neuroendocrine axis, with consequent hypoactivity of certain pituitary functions and a resultant delay in the onset of maturation and senescence."

Aktuelle Gerontol 1977 Oct;7(10):535-8. **Long-term tryptophan restriction and aging in the rat.** Segall P. Growth-retarded rats fed a tryptophan deficient diet at 21 days for periods of **6-22 months were shown to reach normal body weight when subsequently fed Purina Rat Chow. They demonstrated an increased ability over similar aged controls to recover from hypothermia induced by 3-minute whole-body ice water immersion,** were able to bear litters at 17--28 months of age, showed a delay in the age of onset of visible tumors, and indicated an increase in their average lifespan at **late ages. Animals fed on this diet from 3 months of age revealed a similar ability to reproduce at advanced ages, but not as marked as those placed on the diet earlier. The average lifespan (in months +/- the standard error of the mean) of the rats recovering from the long-term tryptophan-deficient diets was 36.31 +/- 2.26 while the control rats survived an average of 30.5 +/- 1.90** months. The last of 8 rats surviving the period of tryptophan-deficiency died at **45.50 months (1387 days) while the last of 14 control rats died at 41.75 months (1266 days). It is hypothesized that some kind of subtle mechanism exerts its** influence on the rats during the period of tryptophan deficiency which caused an accelerated morbidity and mortality as they approached senescence approximately **1 to 2 years after refeeding.** This is parallel to the situation with immature **animals subjected to long-term caloric restriction and then fed on normal diets.**

Mech Ageing Dev 1976 Mar-Apr;5(2):109-24. **Patho-physiologic findings after chronic tryptophan deficiency in rats: a model for delayed growth and aging.** Segall PE, Timiras PS. Long-Evans female rats three weeks, three months and 13-14 months of age were placed on tryptophan-deficient diets for periods ranging from a few months to nearly two years. Growth was interupted during the period of tryptophan-deficiency, but when the animals were returned to a complete diet, they gained weight and grew to normal size. Ability to reproduce, as indicated **by litter production, was present at 17-28 months of age in rats which had been deprived of**

tryptophan, whereas no controls over 17 months of age produced any offspring. Other signs of delayed aging in the experimental group included, at advanced ages, greater longevity, as well as later onset in the appearance of obvious tumors, and better coat condition and hair regrowth. Many of these effects were also seen in pair-fed controls (fed a diet equal in amount to that eaten by the tryptophan-deprived rats, but with 1-tryptophan added). It is hypothesized that tryptophan deficiency delays growth, development and maturation of the central nervous system (CNS), in particular, by decreasing the levels of the neurotransmitter serotonin, for which tryptophan is the necessary precursor. In a parallel experiment, chronic treatment with d, 1-parachlorophenylalanine, an inhibitor of brain serotonin synthesis, from weaning until adulthood, also inhibited growth (body weight) and delayed sexual maturation (age of vaginal opening). These observations suggest that diets deficient in tryptophan or restricted in calories can affect maturation and aging by interfering with CNS protein synthesis, or neurotransmitter metabolism, or both.

Naturwissenschaften 1965 Sep;52(18):519. **[Serotonin-caused muscular dystrophy].** [Article in German] Selye H.

Toxicology 1999 Feb 15;132(2-3):139-46. **Protection against chronic cadmium toxicity by glycine.** Shaikh ZA, Tang W

Biosci Biotechnol Biochem 1998 Mar;62(3):580-3. **Increased conversion ratio of tryptophan to niacin in severe food restriction.** Shibata K, Kondo T, Miki A.

Monogr Neural Sci 1976;3:94-101. **Sex, migraine and serotonin interrelationships.** Sicuteri F, Del Bene E, Fonda C. "Sexual deficiency or frank impotence in man could be due to an imbalance of monoamines, particularly 5-HT, at the mating center level. An absolute or **relative excess of 5-HT seems to antagonize testosterone at the level of the mating center receptors in the brain. Plasma testosterone levels in so-called psychological impotence are normal. When the 5-HT concentration in sexually deficient men is sufficiently decreased with parachlorophenylalanine (PCPA)** treatment and testosterone levels increased following its administration, a vivid sexual stimulation appears in about half of the untractable cases." "Yet the PCPA-MAOI treatment avoids the prostate carcinogenic risk of testosterone administration in aging males, and seems to have euphorizing effects stronger than those expected only from MAOI therapy. Because of the several side effects of PCPA-MAOI testosterone, the present experiments should be interpreted very cautiously."

Hepatology 1999 Mar;29(3):737-45. **Glycine and uridine prevent D-galactosamine hepatotoxicity in the rat: role of Kupffer cells.** Stachlewitz RF, Seabra V, Bradford B, Bradham CA, Rusyn I, Germolec D, Thurman RG.

Eur J Appl Physiol Occup Physiol 1999 Mar;79(4):318-24. **Effect of acute and chronic exercise on plasma amino acids and prolactin concentrations and on [3H]ketanserin binding to serotonin2A receptors on human platelets.** Struder HK, Hollmann W, Platen P, Wostmann R, Weicker H, Molderings GJ. **"The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) has been shown to modulate various physiological and psychological functions such as fatigue.** Altered regulation of the serotonergic system has been suggested to play a role in response to exercise stress." "The present results support the hypothesis that acute endurance exercise may increase 5-HT availability. **This was reflected in the periphery by increased concentration of the 5-HT precursor free TRP, by increased plasma PRL concentration, and by a reduction of** 5-HT2A receptors on platelets."

Epilepsy Res 1999 Jan;33(1):11-21. **Pharmacokinetic analysis and anticonvulsant activity of glycine and glycinamide derivatives.** Sussan S, Dagan A, Bialer M.

Adv Biochem Psychopharmacol 1976; 15:251-65. **Glucocorticoid regulation of the serotonergic system of the brain.** Sze PY. "Glucorticoids at concentrations above 10(-7) M stimulate the uptake of tryptophan by brain synaptosomes."

Neurobiol Aging 1984 Fall;5(3):235-42. **Lifetime brain serotonin: regional effects of age and precursor availability.** Timiras PS, Hudson DB, Segall PE. **"In the rat, regional brain serotonin levels which do not change from 2-30 months of age are increased at 36 months."** "Impaired brain serotonin levels recover moderately but remain lower than controls as late as 36 months, growth is never completely compensated, and norepinephrine levels show a rebound increase."

Kidney Int 1996 Feb;49(2):449-60. **Cytoprotection of kidney epithelial cells by compounds that target amino acid gated chloride channels.** Venkatachalam MA, Weinberg JM, Patel Y, Saikumar P, Dong Z

Am J Physiol Lung Cell Mol Physiol 2000 Aug;279(2):L390-8**. Dietary glycine blunts lung inflammatory cell influx following acute endotoxin.** Wheeler MD, Rose ML, Yamashima S, Enomoto N, Seabra V, Madren J, Thurman RG.

Am J Physiol 1999 Nov;277(5 Pt 1):L952-9. **Production of superoxide and TNF-alpha from alveolar macrophages is blunted by glycine.** Wheeler MD, Thurman RG.

Stroke 1991 Apr;22(4):469-76. **Identification of capric acid as a potent vasorelaxant of human basilar arteries.** White RP, Ricca GF, el-Bauomy AM, Robertson JT **"To determine whether naturally occurring fatty acids, especially saturated ones, might act directly as vasodilators, segments of human basilar arteries and umbilical arteries were precontracted submaximally with prostaglandin F2 alpha and then exposed to different saturated fatty acids (C4 through C16) or** unsaturated fatty acids (C14:1, C18:1, C18:2, and C18:3) at concentrations from 4 microM to 4 mM. The results showed caprate (C10) to be the most potent vasorelaxant and basilar arteries to be more responsive (EC50 = 63 microM) than umbilical arteries (EC50 = 780 microM). **Caprate also inhibited contractions elicited by KCl, serotonin, and the thromboxane analogue U46619.**"

Neurochem Res 1978 Jun;3(3):295-311. **Adaptive changes induced by high altitude in the development of brain monoamine enzymes.** Vaccari A, Brotman S, Cimino J, Timiras PS.

Growth Dev Aging 1991 Winter; 55(4):275-83. **Effect of aging and diet restriction on monoamines and amino acids in cerebral cortex of Fischer-344 rats.** Yeung JM, Friedman E.

Proc Natl Acad Sci U S A 1992 Jul 15;89(14):6443-6. **Platelet activation by simultaneous actions of diacylglycerol and unsaturated fatty acids.** Yoshida K, Asaoka Y, Nishizuka Y "Several cis-unsaturated fatty acids such as oleic, linoleic, linolenic, eicosapentaenoic, and docosahexaenoic acids added directly to intact human platelets greatly enhance protein kinase C activation as judged by the phosphorylation of its specific endogenous substrate, a 47-kDa protein." "**In the presence of ionomycin and either 1,2-dioctanoylglycerol or phorbol 12-myristate 13-acetate, the release of serotonin from the platelets is also remarkably increased by cis-unsaturated fatty acids. The effect of these fatty acids is observed at concentrations less than 50 microM. Saturated fatty acids and trans-unsaturated fatty acids are inactive."** ". . . cis-unsaturated fatty acids increase an apparent sensitivity of the platelet response to Ca2+. The results suggest that cis-unsaturated fatty acids, which are presumably produced from phosphatidylcholine by signal-dependent activation of phospholipase A2, may take part directly in cell signaling through the protein kinase C pathway."

Jpn J Physiol 1969 Apr 15;19(2):176-86. **Lipolytic action of serotonin in brown adipose tissue in vitro.** Yoshimura K, Hiroshige T,

Itoh S

Hepatology 2000 Sep;32(3):542-6. **Glycine prevents apoptosis of rat sinusoidal endothelial cells caused by deprivation of vascular endothelial growth factor.** Zhang Y, Ikejima K, Honda H, Kitamura T, Takei Y, Sato N

Mol Pharmacol 1999 Sep;56(3):455-63. **Dietary glycine and renal denervation prevents cyclosporin A-induced hydroxyl radical production in rat kidney.** Zhong Z, Connor HD, Yin M, Moss N, Mason RP, Bunzendahl H, Forman DT, Thurman RG