Ray Peat's Newsletter

It is difficult to get a man to understand something when his salary depends on his not understanding it. Upton Sinclair

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The GABA system, defenses, and tissue renewal

Inhibition is an active process, that isn't limited to the effects of specific inhibitory nerves. In recent decades, the amino acids gamma-aminobutyric acid (GABA) and glycine (alpha-aminoacetic acid) have been identified as "inhibitory transmitters," acting on specific receptor proteins to inhibit a nerve or muscle.

This has led to increasing understanding of some sedative and anti-convulsive drugs, but it neglects the real biological nature of inhibition and excitation. The amino acid "transmitters" are just part of a much larger system of cell regulation.

To understand healing and regeneration and other developmental and formative processes I think it's necessary to consider the issues of cellular and organismic stability and instability, inhibition and excitation, in the most thorough and general way.

Cell interactions generally involve mutual stabilization. Nerves stabilize muscles, muscles stabilize nerves, and nerves stabilize other nerves. Losing their normal intercellular communications, cells become hypersensitive and hyperactive.

When an excess of stimulation threatens to damage a tissue, processes of inhibition can restore stability. But when cells are damaged irreparably, stimulation can induce other cells to grow and multiply to replace the lost cells. The growth continues until inhibitory processes are restored.

Protective inhibition is one of the most important principles in biology. Heart disease, cancer, anxiety, allergies, epilepsy, degenerative nerve diseases, endocrine disorders, inappropriate inflammation and shock all involve defects of protective inhibition.

The agents of protective inhibition increase survival, along with mental abilities and metabolic rate. Too often the excitants suppress energy production while increasing the need for energy, leading to impaired functions and failure of restorative processes.

For thousands of years people have understood the value of herbal sedatives, soporifics, and anti-convulsants, but modern neurology's ideological commitments have retarded the scientific development of therapies to enhance protective inhibition.

J.C. Bose, working in England and India at the end of the 19th century (radio, microwave, vegetable electricity, the electric response of inorganic substances), showed that plant cells and animal cells have very similar reactions, and that similar processes of excitation, fatigue, and recovery also occur in substances such as metal. Drugs and poisons could be shown to have effects on plant material and metals,* analogous to their effects on animals.

Michael Polanyi's work with crystals in the 1920s showed that merely wetting a surface affected the physical properties of the whole crystal.

His understanding of sensitivity, irritability, fatigue, memory and other biological processes disturbed the academic biologists, who were committed to a certain biological doctrine in which membrane electricity and genes explained everything, and had nothing directly to do with general properties of matter.

C.S. Sherrington in England, and S. Ramón y Cajal and R. Lorente de Nó in Spain developed the idea of the synapse as a point of interaction between nerve cells, which formed the basis for reflexes. A nerve would transmit its excitation to a muscle or another nerve in an all-or-none manner, that is, the reaction, if it happened at all, didn't correspond to the strength of the stimulation. The reductionist ideology was already, at the beginning of the 20th century, reducing biological interactions to simple yes or no, black or white, terms. The infinite complexity of the material substrate was eliminated from direct participation in the scheme of life by definition.

Like Descartes, Sherrington and his followers saw reflexes as something separate from consciousness. "Between reflex [automatic] action and mind there seems to be actual opposition. Reflex action and mind seem almost mutually exclusive - the more reflex the reflex, the less does mind accompany it." "The mental action lies buried in the brain, and in that part most deeply recessed from outside world that is furthest from input and output."

Later in the 20th century, biologists were still identifying consciousness with graded processes, that are too subtle to be accounted for by the all-or-none synaptic interactions of nerves.

In 1863, I.M. Sechenov had already published a book, Reflexes of the Brain, arguing that all aspects of the mind, including thoughts and feelings, directly involve nervous activity.

A Russian biologist, Vvedensky (1902), demonstrated that weak stimuli and strong stimuli applied to a nerve produced very different effects in the muscle activated by the nerve. "Wedensky *[German spelling]* found that at a certain stage in the fatigue or narcosis of a muscle-nerve preparation, a series of strong or rapidly recurring stimuli may produce a small initial contraction only (Anfangszuckung), whereas a series of weak or slowly recurring stimuli produce a continued tetanus." (J Physiol. 1913 July 18; 46(4-5): 384-412. Wedensky inhibition in relation to the `all-or-none' principle in nerve. E. D. Adrian.)

Another Russian biologist, P.N. Nasonov, using a variety of cell types, including algae, showed that an excessive stimulation that weakened a cell's ability to respond electrically also weakened its resistance to other environmental factors, and that the right kind of stimulation could increase the cells' resistance to stress. These ideas were expanded and applied to human health issues by the cardiologist F.Z. Meerson, whose laboratory investigated the protective and therapeutic effects of the complex multi-level inhibitory anti-stress system.

The Sherrington tradition, the synapse-membrane all-or-none school of neurology, was complemented by the hormone-receptor-gene-activation school of endocrinology, and by parallel reductionist approaches to embryology. None of these traditions produced anything useful, except in the sense that the receptor doctrine was perfectly suited to pharmaceutical advertising.

The all-or-nothing reflex doctrine reinforced an interpretation of the cell in which a barrier membrane at the cell surface momentarily opens when it's appropriately stimulated, allowing excluded sodium ions to enter, modifying the electrical field and causing a reaction that "propagates along the

nerve like a line of falling dominoes." As Gilbert Ling has pointed out, that doctrine isn't based on real science--for example, the resting membrane doesn't exclude sodium ions. Many things account for the fact that it continues to be taught, but I have talked about that previously. The fact that "membrane depolarization" makes it easy to conceptualize propagation of the excited state as an all-or-none process appeals to the reductionist mentality. But more than 70 years ago, A.V. Hill's measurements of heat production during nerve activity demonstrated that the wave of excitation passes through the entire substance of a nerve, rather than being a matter of "falling dominoes" in the superficial plasma membrane.

It is in the substance of the nerve cytoplasm itself that the protective inhibitory processes occur. In the all-or-none membrane theory in which reflexes are produced by synaptic events, the inhibitory GABA receptors are described as membrane receptors. The basic theory of membrane receptors is that, since the membrane is a barrier, the receptor allows hormones or transmitter molecules to act on the cell without having to enter the cell.

But when a molecule resembling an inhibitory steroid was made water soluble, so that it couldn't enter cells, it was unable to activate the GABA receptor associated with the membrane. When it was presented to the receptor from the cytoplasmic side, however, it was able to modify the GABA receptor. (Akk, et al., 2005.) The normal oil soluble neurosteroids tend to remain in the cells when they are made there, or to enter them spontaneously from the bloodstream, so the postulated function of "membrane receptors" would seem to be wrong. The GABA receptor has been found to associate with the internal cytoskeletal proteins. This is significant, because the glutamate transporter, that participates in restoring inhibition, has recently been found to be associated with a cytoskeletal protein (GFAP) (Sullivan, et al., 2007). This protein is known to be induced by progesterone.

The membrane theory is an attempt to explain the coordination of events that happen in a cell when it is stimulated. The different phases of heat change observed by Hill and others subsequently can only be explained as a phase change in the bulk of the cellular substance, not just a ripple in a superficial lipid film. Different molecular conformations and associations have different levels of organization, that represent structural energy, and different arrangements are separated by small energy barriers. Mutual stabilization of molecular systems gives way to a cooperative phase transition and the establishment of a new organization at a slightly different energy level when stimulation overcomes the energy barrier. The domino analogy is inadequate because the change is three dimensional. Proteins, lipids, sugars, water and ions participate in these cooperative structural changes.

A student of Pavlov's, P.K. Anokhin, discussed a variety of reasons for believing that the information transmitted by the activated state of an axon was complex, rather than a single binomial bit. Since his time many kinds of information have supported and enriched that view. Cellular interactions are always complex, and the all-or-none reflex is an extremely misleading abstraction.

Drugs and natural regulatory substances associate with certain proteins, and those proteins are identified as their "receptors." Since the technique of "knocking-out" the genes for specific receptors has been developed, it has become apparent that the regulatory substances are often able to act without the protein that had been known as the receptor. (For example, Reddy and Apanites, 2005.) Other proteins may then be identified as additional receptors. Occasionally, the

condition of the phospholipids and fatty acids, or the preceding state of the cell, is recognized as having a crucial role in the cell's response. But this holistic view hasn't been useful to the pharmaceutical industry.

Interacting cells are participating in a developmental process, in which their structures and metabolisms are regulating themselves in relation to their situation, which is influenced by events in the life of the whole organism. An organism's anticipation and learning contribute to the renewal of tissues and resistance to stress. Unavoidable stress damages or kills nerve cells, and the resulting mobilization of defenses can lead either to successful defense and recovery, or inadequate defense and chronic disease.

Once the protective function of inhibition is recognized, there are many things that can be done to support the organism's recuperative processes.

Pavlov and his followers began applying the principle of protective inhibition to medicine, and it has been used to treat neuroses, brain injuries (even "brain death"), and various organic diseases. Pavlov observed that individual differences in nervous stability could cause the therapeutic dose of a sedative to vary several-fold. Prolonged sleep was found to be a very powerful therapy, that could even reverse age-related changes, but drugs such as the barbiturates were too toxic for extensive use of the therapy. Sleep induction by electrical brain stimulation was investigated as an alternative. Subsequently, Meerson's group investigated the metabolic and biochemical factors involved in protective inhibition. Although Meerson's research focused on the heart, the factors he identified apply to other organs and tissues. The progressive commercialization of medical research, however, has submerged those integrated organismic approaches to therapy.

Using the general approach of Pavlov and Meerson, it's now possible to achieve a high degree of protective inhibition without using toxic drugs, but it's important to minimize the chronic factors that create a susceptibility to uncontrolled excitatory states.

The toxic effects of excessive stimulation involve suppression of respiratory energy production. Excitation releases fatty acids from tissue phospholipids, and the polyunsaturated fatty acids (PUFA) increase excitation, decrease the inhibitory actions of the GABA system, and interfere with energy production by the mitochondria, leading to the wasteful conversion of glucose to lactic acid. Excitation increases the production of free radicals by the mitochondria themselves (Duan, et al., 2007). Just eliminating most PUFA from the diet decreases the risks of excitotoxicity.

DHA and arachidonic acid increase the excitatory effect of glutamate on its receptor (Yeh, et al., 1995), and decrease the uptake of glutamate by the protein that binds it to stop the excitatory process (Yu, et al., 1986). These fats cause swelling of mitochondria and cells, and increase vascular permeability. Saturated fats don't have those excitatory effects.

Fish oils and other omega -3 oils are being promoted as treatment for many diseases, especially heart disease, arthritis and other inflammatory diseases, and depression. They do have an antiinflammatory effect, at least in the short term, partly associated with their inhibition of prostaglandin synthesis, but their antiinflammatory effects have been found to result from their oxidized products (Chaudhary, et al., 2004), which have many toxic effects. Although claims are made regarding their beneficial effect on the circulatory system, there are good reasons to think that they contribute to atherosclerosis (for example, Wang and Oram, 2002, 2005). And they suppress the immune system and thyroid function.

The PUFA (especially the omega -3 fatty acids) spontaneously decompose into a variety of toxins, and arachidonate is also enzymically converted into prostaglandins, some of which exacerbate the excitatory damage (Pepicelli, et al., 2005); aspirin's neuroprotective effect (Riepe, et al., 1997) is probably partly caused by inhibiting prostaglandin synthesis. Besides the prostaglandins, other mediators of inflammation including nitric oxide and interleukins are produced by excessive excitation, as cells lose their ability to retain magnesium, and to control excitatory intracellular calcium.

Nitric oxide, associated with unbalanced excitation, is involved in the nerve damage of epilepsy, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease. An energy deficit increases excitation and cellular calcium uptake, increasing nitric oxide synthesis (Schulz, et al., 1997). Nitric oxide increases the ratio of glutamate to GABA ("the excitotoxicity index"), (Demchenko & Piantadosi, 2006), while lowering mitochondrial energy production.

The PUFA increase the susceptibility to excessive serotonin in the nervous system. One of the functions of the GABA system is to inhibit serotonergic nerves (Calogero, et al., 1988; Kaura, et al., 2007). Eating a diet with a very low tryptophan content, and lacking PUFA, can support that function of the GABA system. The tea amino acid, theanine, suppresses serotonin by supporting the effects of GABA. Three of the major types of antidepressant also protect against glutamate/aspartate-induced nitric oxide formation and nerve cell damage (Li, et. al., 2006).

It's important not to confuse the process of inhibition with psychological depression, which often involves an inability to inhibit the stress responses. The GABA system restrains the production of cortisol, which is typically increased in depression. GABA-supporting drugs that had been used to treat epilepsy are turning out to have antidepressive, mood-elevating effects.

The diazepam type of antianxiety, antiseizure drug activates the GABA system, and this system is intimately involved with the synthesis of steroids. Several varieties of that type of sedative increase the synthesis of the neurosteroids, derived from progesterone. Progesterone and some of its metabolites protect the mitochondria, while acting with GABA to increase the state of inhibition.

During the menstrual cycle, the GABA system is weaker during estrus, when estrogen's effect is high. Progesterone is associated with a higher level of GABA, and the two substances have many of the same effects on behavior.

Estrogen's excitatory effects can be seen in all types of tissue. In the brain, it tends to increase physical activity and loquacity, to increase the susceptibility to seizures, and sometimes to cause chorea, involuntary random jerking and writhing movements.

It is antagonistic to the GABA system, and promotes the action of excitatory transmitters, and increases formation of nitric oxide and prostaglandins. In cancers that are promoted by estrogen, GABA, like progesterone, inhibits cell division. It is an antiproliferative agent in normal tissues, too, opposing estrogen's effects and supporting progesterone's.

Drugs (such as piracetam) that promote GABA's effects are called "nootropins," or cognitive enhancers, and have been used to treat brain damage and mental retardation. GABAergic agents also protect the thymus gland and improve immune functions.

The first serious approach of the pharmaceutical industry to treating Alzheimer's disease was based on increasing the excitatory action of acetylcholine. When it became apparent that those drugs weren't helpful,

there was a less publicized trial of some drugs that block the effects of acetylcholine. If white doesn't work, they try black. The industry's function, exercised through medical and science journals, and medical schools and universities, is to sell new products, and that has often made it necessary for the industry to suppress approaches that would make their products unnecessary. As the head of a drug company told me, a drug that cures quickly isn't a good drug; a good drug is one that the patient has to keep taking for the rest of his life.

Progesterone's inhibitory function was already well established in the 1940s, by the work of Selye and Lipshutz, for example. In the 1950s and 1960s its effects on brain development and intelligence were established. In vitro studies showed that it was a nerve growth factor, and it was identified as a hormone that caused new brain cells to develop in an area of birds' brains as their ability to sing developed. Katherina Dalton's clinical experience supported the animal work which showed that prenatal exposure to higher levels of progesterone improved mental functioning later in life.

Progesterone supplementation can sometimes cause complete recovery from dementia and motor neuron diseases.

After many years of animal experiments showing that progesterone promotes recovery from traumatic brain damage (Cutler, et al., 2007; Stein, 2007), it is now being used to treat people following severe brain injury (Wright, et al., 2007).

Neither progesterone nor GABA stimulates cell multiplication, yet they improve the regenerative process. Their effects are the result of preventing premature cell death, and promoting normal differentiation and maturation. In various kinds of degenerative brain disease, the connective tissue glial cells in the brain become too numerous, while the nerve cells decline. Excitatory processes cause new cells to be formed, and with the proper energetic and inhibitory support the new cells can mature into functional nerves, that maintain or restore the existing systems and functions.

Certain kinds of excitation cause new nerve cells to be formed (neurogenesis). The enzyme that liberates arachidonic acid (phospholipase A2, which also releases docosahexaenoic acid DHA) from tissue structures, creates a type of phospholipid that is slightly more water-soluble and mobile because of the removal of that fatty acid. These are called lysophospholipids, because they were originally identified as a substance that lysed red blood cells. The enzymes that produce them are activated by many things, including free radicals, increased calcium, and the shift of balance toward excitation (Birkle, 1992), away from dominance of the GABA system.

The lysophospholipids stimulate, among other things, neurogenesis (Fukushima, 2004; Harada, 2004; Ishii, et al., 2003; Dubin, et al., 1999). The arachidonic acid that is liberated in its formation excites cells, in a process that can get out of control if the inhibitory GABA system is weak. It can produce gliosis from excessive stimulation of cell division combined with a lack of the factors such as GABA needed for maturation into nerve cells, and it can kill nerve cells, by interrupting their energy production. The accumulation of this and related fatty acids with aging is a problem.

The DHA and other polyunsaturated fatty acids released by cellular excitation cause mitochondrial damage and edema, but saturated fatty acids don't have those effects (Chan and Fishman, 1980, 1982; Chan, et al., 1988; Hillered and Chan, 1988, 1989).

Alexis Carrel, with a famous experiment begun in 1912, showed that animal tissues kept in culture dishes with frequent (daily)

changes of the growth medium didn't age, and he suggested that changes in the fats in the body accounted for aging. Lately the gene-technology people have said fraud was involved in Carrel's experiments, but many other kinds of experiment produced similar results. For example, Hans Selye found that frequent changes of fluid prevented aging of tissue growing inside an implanted capsule.

Polezhaev's discovery that mammalian tissues can be induced to regenerate by the presence of degenerating tissue (which releases the breakdown products of phospholipids and proteins) is consistent with the recent demonstrations that stem cell growth is activated by fatty acids and phospholipids.

The saturated fats, rather than simply lacking the toxic and excitatory properties of the polyunsaturated fats, are being shown by many types of research to have protective, inhibitory, and restorative actions.

The medium chain triglycerides (MCT, usually made from coconut oil) are easily oxidized by mitochondria, and are often used to produce ketosis, to prevent seizures. A high-fat diet has been used since about 1920 to control epilepsy, but there is no generally accepted explanation for its effect. A ketogenic diet produces acetone, acetoacetate, and beta-hydroxybutyrate ("ketone bodies") and these are protective against seizures (Rho, et al., 2002). Besides providing energy to mitochondria, hydroxybutyrate is structurally close to GABA. Other close analogs, gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol, clearly act as regulatory substances, rather than as mere energy sources, though mitochondrial energy supply is an important issue in seizures. Even acetate itself is protective (Urion, et al., 1979).

A feature common to many antiseizure chemicals is a series of saturated carbon atoms, for example valproic acid (2-propylpentanoic), valeric acid (pentanoic acid), dipropylacetic acid, isoleucine (2-amino-3-methylpentanoic acid), leucine (2-amino-4-methylpentanoic acid).

The main difference between metabolism of glucose and metabolism of fat for energy is that fat can't be metabolized into lactic acid, while glucose and fat can both be metabolized to carbon dioxide. When mitochondria are damaged, cells compensate by producing and excreting lactic acid.

Alzheimer's disease has been described as "diabetes of the brain," because the demented brain uses glucose and oxygen very slowly. The easily metabolized medium chain triglycerides can improve mental functions in Alzheimer's patients (Reger, et al., 2004).

Although diabetes is described as an inability to use glucose, diabetics usually have increased lactate in their blood, indicating that glucose is being used wastefully, at the same time that some energy is produced from fat. Mitochondria damaged by chronic exposure to PUFA have a low rate of oxygen use and energy production.

In old age, and sometimes in younger people, mitochondria lose some of their DNA, and are unable to produce the proteins needed for full metabolic activity. In younger people, a type of mitochondrial defect causes seizures and lactic acidosis. The production of lactic acid tends to raise the intracellular pH (especially when carbon dioxide isn't being produced) while it tends to lower the blood's pH. High intracellular pH is excitatory. The "genetically" defective mitochondria can be replaced by genetically normal mitochondria if the ketone bodies are provided (Santra, et al., 2004). A similar restoration of normal mitochondria can be achieved in old people's muscles through a program of "concentric" contractions.

Other GABAergic agents are able to functionally restore damaged mitochondria,

but in these studies, the quality of the DNA wasn't investigated. Piracetam intensifies oxygen consumption in damaged mitochondria, for example following injury or oxygen deprivation, especially in older animals. The restoration is permanent, so in this case the substance isn't acting just as a more easily metabolized source of energy, as was believed to be the mechanism in the case of the ketone body supplement.

Many people still believe that increasing oxygen consumption necessarily increases free radical activity and shortens the life-span, and that the life extension produced by caloric restriction results from reduced oxygen consumption. The fact that estrogen suppresses mitochondrial oxygen consumption is being used to justify using it to treat aging and dementia. But caloric restriction doesn't reduce oxygen consumption per gram of tissue, and sometimes increases it. Uncoupling mitochondria, so that they consume more energy without producing more ATP, appears to produce an extension of lifespan approximately equal to the increased rate of energy and oxygen consumption (data discussed in Speakman, 2003). Increasing the metabolic rate has effects similar to restricting calories. Supplementing thyroid, increasing saturated fats such as MCT and coconut oil, and restricting polyunsaturated fats, can increase the metabolic rate.

Piracetam (like other GABAergic agents) very effectively decreases lipid peroxidation (Novikov, et al., 1996), despite increasing metabolic activity. While decreasing oxidative damage and increasing ATP production, it also lowers the activity of the cells' important antioxidant enzymes (Keil, et al., 2006). When a cell isn't being damaged, those adaptive enzymes aren't required to be so active. (Many publications argue that certain products are "beneficial because they increase the antioxidant enzymes," but in fact almost any kind of injury will increase those protective enzymes.)

If mitochondria aren't damaged, for example in healthy young animals, piracetam doesn't greatly increase their activity. It simply restores them when they are damaged.

The mitochondria, besides producing energy and regulating calcium and other minerals, are the source of the GABAergic steroids. Since mitochondria contain "valium receptors" or GABA receptors, their high concentration in the region of synapses has probably sometimes been interpreted as showing "membrane receptors." But wherever they are, mitochondria are powerful agents of cellular interactions and regulation.

The carbon dioxide produced by mitochondria is involved in regulating ions and cellular electrical polarization, and protecting against free radicals. The energized and polarized cell retains magnesium and potassium, and excludes sodium and calcium. Increasing magnesium favors the protective inhibitory state, and is sometimes given intravenously to stop seizures. Adequate sodium in the diet is necessary for efficient retention of magnesium, and sodium is also required for the binding of glutamate. Lithium can replace sodium in activating glutamate removal (Menaker, et al., 2006), and it protects the brain against excitotoxicity (Chuang, 2004).

Breathing carbon dioxide has been used to stop seizures, and the drug, acetazolamide, which increases the body's retention of CO2, is sometimes used for epilepsy. Increased carbon dioxide protects the brain against a variety of factors (e.g., Simon, et al., 1993), and is probably involved in glutamate uptake.

Niacinamide, one of the B vitamins, happens to have GABAergic sedative activity, but it also has two other important effects. It can suppress lipolysis and lower circulating free fatty acids, reducing their interference with the use of glucose, and when the

mitochondria are already damaged, it can reduce the formation of lactic acid, by allowing the sugar to be fully oxidized. Forming the coenzyme NAD, niacin is responsible for maintaining an appropriate balance between oxidation and reduction (as the main cellular reductant), protecting cells from oxidative stress. (Shen, et al., 2003; Singh, et al., 2005; Kang, et al., 2006; Watanabe, et al., 2006; Kao, et al., 2007; Su, et al., 2007). The glutamate transporter must be kept in the reduced state to bind glutamate and stop the excitatory process (Trotti, et al., 1997).

Maintaining an adequate supply of glucose is directly protective against excitotoxicity (e.g., Flavin, et al., 1993), and helps to prevent stress reactions systemically.

Thyroid hormone (which has a reciprocal relation to estrogen) produces many relaxant effects, such as rapid relaxation after the Achilles tendon reflex contraction, reduced blood pressure, and deeper sleep, but its supportive effects on the GABA system are seldom considered in relation to therapies. It is essential for producing carbon dioxide, the neurosteroids, and ATP. Magnesium is retained in cells largely by its association with ATP, and it helps to keep the ATP level high. Thyroid is needed for preventing excessive estrogen stimulation, and for controlling adrenaline and serotonin. But it also directly interacts with the GABA system, supporting the protective inhibitory functions (Zamoner, et al., 2006; Gilbert, et al., 2007; Ortiz-Butron, et al., 2003).

Inhibitors of estrogen synthesis are being considered for use in controlling epilepsy (Reddy, 2007), but aspirin and progesterone and thyroid can produce similar results.

When mitochondria are functioning fully, either glucose or saturated fats can safely provide energy. Some glucose or saturated fat can be converted to polyunsaturated fats, that can be used as regulators or signals, for example to activate the formation of stem cells. But those PUFA don't create disruptive cascades of increasing excitation or inflammation or excessive growth, and, from the evidence of animals that are fed fat free diets, or diets lacking omega -3 and omega -6 fatty acids, they aren't toxic to mitochondria.

When a healthy cell is excited, the mitochondria become more active, and their energy needs may exceed the amount of glucose available, leading to the formation of ketone bodies. Glucose deprivation seems to be a fundamental signal of stress, and the formation of ketone bodies is possibly the most primitive defensive reaction to stress. They protect nerves from excitatory oxidative damage (Noh, et al., 2006), inhibit mitochondrial production of reactive oxygen species during excitation (Maalouf, et al., 2007) and inhibit tumor growth and lactate production (Magee, et al., 1979). Increased thyroid hormone can increase ketone formation (Riou, et al., 1980; Bartels and Sestoft, 1980).

The idea of synaptic membrane receptors often leads people to think of cellular inhibition in terms of raising a cell's threshold for producing an all-or-none membrane response to stimulation. But the inhibitory and excitatory systems interact at all levels of function and structure, reciprocally modifying each other.

In response to signals for excitation or inhibition, for example, the quantity of GABA and GABAergic steroids such as progesterone will change, in response to increases or decreases in the enzymes that produce or eliminate them, and changes in concentrations of precursor molecules. The quantity and sensitivity of the various types of "receptor" will change. Proteins that bind and inactivate GABA and other regulators will change in quantity and effectiveness. The rate at which energy is produced will change, along with the rates of cellular reconstruction and

decomposition. The cells' metabolic changes will produce signals that affect adjoining cells and the organism's physiological processes, including circulation, respiration, and readiness for stress.

In the "normal" course of aging, good tissues atrophy, and may be partly replaced by fibrotic tissues, and in that environment, tumors and disorganized structures of various kinds develop. The highs and lows, the daily cycles of mental and physical activity, tend to be leveled, as the ability to produce metabolic energy declines.

The polyunsaturated fats suppress energy production, and that suppression is aggravated by their excitatory or inflammatory effects, which lead to increased excitation by other intrinsic factors such as estrogen, cytokines, serotonin, and peptide hormones, that intensify the problem of maintaining energy production. Stimulation, without corresponding appropriate inhibition and adequate energy, skews the path of development, toward aging and sickness.

When each cell is fully energized and stabilized, it is sensitive and responsive to its surroundings, supporting the organism's adaptability.

Although caffeine is a stimulant that can offset the sedative effects of GABA, it also functions as a neuroprotectant, protecting against some of the effects of glutamate (Chinopoulos, et al., 2004). It is also a very good source of two other protective factors, magnesium and niacin. "French-roast" (dark) coffee is an especially rich source of niacin, which might be responsible for the "French paradox," the low incidence of heart disease in a country that doesn't follow the AHA's "heart protective diet."

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