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Restoration of cellular energetic balance with L-carnitine in the neuro-bioenergetic approach for cancer prevention and treatment

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Summary Mitochondrial research has contributed to two paradigm shifts in oncology — Warburg's glycolytic metabolism and the relationship between mitochondrial function and mutagenesis. Mitochondrial dysfunction is a common phenotype in aging and cancer. Decline in mitochondrial function is due to the accumulation of mutations in mitochondrial DNA.

We have hypothesized a neuro-bioenergetic concept in cancer prevention and treatment to constructively restore three physiological imbalances of cancer patients: membrane hyper-excitability, energy depletion and the build up of extra-cellular adenosine molecules. We have proposed the use of membrane-calming substances to reduce energy consumption and to restore the normal cellular energy metabolism. Based on our theory, L-carnitine's dual effect of enhanced energy production and excitatory neurotransmitter modulation should make it an ideal nutrient for cancer prevention and treatment. L-carnitine, its derivatives and other mitochondrial protectors/enhancers improve metabolic function, energy and detoxification. In combination with other membrane calming agents, L-carnitine could help reverse the membrane hyper-excitability to overcome a neuro-bioenergetic imbalance and can be used as a relevant and effective approach for cancer prevention and treatment.

Introduction

The so-called ''War Against Cancer'' proposed and directed by the cancer research community has focused heavily on destructive, inhibitive strategies toward cancer cells, their receptors, growth factors, energy metabolism, glycolysis, angiogenesis, fatty acids synthesis and many other identified pathways of carcinogenesis in order to prevent and treat cancers. There has been limited attention to constructive (pro-health, pro-body), non-toxic approaches in understanding and managing

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cancers as degenerative and aged-related human disorders.

In general, the improvement in cancer prevention and treatment has been linked to preventive intervention, early diagnosis and treatment, and changes in lifestyle. However, pharmaceutical treatments are responsible for only a small fraction of cancer cures [1]. Moreover, objective clinical responses to conventional treatment may not translate into substantial improvement in overall survival [2].

Nobel prize-winner Carlo Rubbia maintains that only a billionth of the world is actually made of matter and the rest is made of energy. In our previous publications, we have proposed and substantiated cancer as a pathology of disruption, cessation or distortion in the cellular information and energy fields. The major causes of these events are environmental and endogenous toxins (mainly in sub-toxic concentrations), chronic infection and ionizing radiation that induce membrane hyper-excitability leading to depletion of cellular energy and excess extra-cellular adenosine [3].

Cancer cells have similar properties to neuronal progenitor cells that are stimulated by glutamate. The hyperexcitability leads to a disparity between energy consumption and supply. These changes are triggered by such hypoxia-induced stimulants as an increase in cytoplasmic free calcium, a decrease in adenosine triphosphate (ATP) and extracellular accumulation of adenosine produced by ATP breakdown [4].

The cells try to survive in this hostile environment with compensatory and adaptive mechanisms leading to transformation, proliferation and migration similar to organo-morphogenesis in embryogenesis, the wound-healing process or the restorative reaction in neurotrauma and/or excitotoxic neurological injuries [5].

Energy balance, defined as the integrated effects of diet, physical activity, environment and genetics on growth, function, adaptation and body weight over the life course, has been a recent focus for understanding the chronology of many chronic diseases. Research from many sources supports the positive influence of physical activity, low toxin environment, green tea, polyunsaturated fatty acids (PUFA) and other dietary patterns on cancer risk and prognosis. However, the concepts of energy enhancement, dietary improvement and detoxification remain of little interest to the conventional cancer research community.

Adverse changes in energy balance are considered to be a major factor underlying many of the pathways involved in cancer initiation and progression. In this article, we will provide evidence for using an energy metabolism restorative approach in cancer prevention and treatment.

Mitochondrial dysfunction and cancer

The mitochondria are widely recognized as the main source of cellular ATP, producing 90% of the cell's energy. This energy organelle is also intimately involved in the life and death of the cell, capable of integrating pro- and anti-apoptotic signals and committing the cell to apoptosis. It is a critical integrating center for control of carbon, nitrogen and oxygen metabolism and in Ca^{2+}, Fe^{2+} and Cu^{2+} storage.

Mitochondrial research has contributed to two paradigm shifts in oncology. The first one was the pioneering research done 80 years ago by Warburg showing that cancer cells often rely heavily on glycolytic metabolism, even in the presence of an adequate oxygen supply [6]. The molecular genetic basis of this phenomenon remains an intriguing subject for current research [7,8]. Tumors have significantly higher energy demands than normal cells. Because of this, they often employ alternative energy production including glycolysis, the anaerobic breakdown of glucose into ATP.

The second paradigm shift in oncology is the greater understanding of the relationship between mitochondrial function and mutagenesis. The mitochondria provide the energy to sustain life, but also the signals of their own demise. Apoptosis is a requisite for the physiological or therapeutic elimination of cancer cells. Researchers believe that cancer cells require mitochondrial energy to avoid apoptosis, which contributes to their replicative potential and limits the efficacy of cancer chemotherapy [9].

Mitochondrial dysfunction is a common phenotype in aging and cancer. An interesting clue to the molecular mechanisms underlying age-associated cancers is the apparent defect in mitochondrial function. Studies have established that the decline in mitochondrial function is due to the accumulation of mutations in mitochondrial DNA. These observations suggest that the mitochondrial dysfunction that accompanies aging may exert a major influence on carcinogenesis [10].

Mitochondria are involved in a strikingly diverse range of disease processes. Primary genetic disorders fall into two broad classes involving deficiencies in either nuclear or mitochondrial genes. As early as 1988, Scholte reported over 60 human diseases with defects in nuclear genes encoding mitochondrial functions [11]. There are currently 129

nuclear gene defects associated with mitochondrial disorders.

The ability of certain tumor cells to withstand either chronic hypoxia or chronically elevated oxidative stress is linked to alteration of protein kinase cascades involving cellular function and division. It must ultimately be possible by the alternative production of ATP, and this is one of the hallmarks of cancer [12].

In the last decade, several reports have correlated defects in mitochondrial energy production as well as mutations in mitochondrial DNA associated with various human cancers [13]. Although the role of these mutations in cancer progression is poorly understood, some reports have shown increased invasive behavior in human lung carcinoma cells carrying mitochondrial dysfunction [14].

Fatty acid metabolism/synthesis abnormalities in cancer

One major form of energy production is through essential fatty acid/phosphate production via ATP synthesis in beta-oxidation in the mitochondria (Fig. 1). Fatty acid synthase (FAS) is the sole enzyme responsible for the de novo synthesis of fatty acids from carbohydrates.

Studies by Pizer et al. have found elevated levels of FAS and correspondingly increased fatty acid synthesis and abnormal fatty acid utilization in cancer. Recent studies have shown that the FAS inhibitor cerulenin is selectively cytotoxic to proliferative cell lines derived from human subjects. This data suggests that the fatty acid synthesis pathway is a potential target for oxidative therapy development [15]. FAS is highly expressed in common human tumors [16]. Also, it is found that proliferative cells can retain dependence on endogenous fatty acid levels and thus support the notion that FAS inhibitors may be useful in treating cancer *in vivo*. Targeting FAS has also been suggested as an effective anticancer approach [16,17].

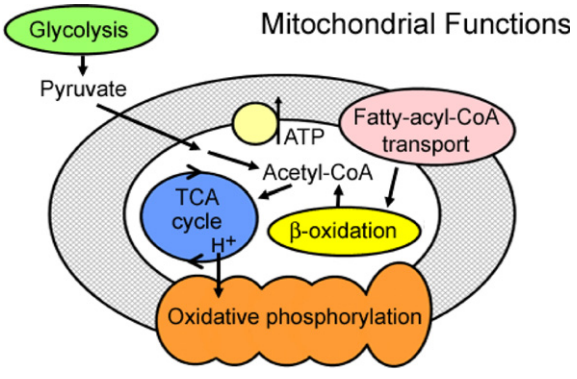

Figure 1 Normal cellular energy metabolism.

Despite research suggesting that inhibiting FFAs may be a promising antitumor immune therapy, there has been no successful cancer treatment modeled on FFA inhibition. Moreover, some epidemiological and basic research has shown the positive roles of an essential fatty acid-rich diet in cancer prevention [18,19].

Given the facts that mitochondrial dysfunction and energy depletion may play a role in carcinogenesis, we speculate that the synthesis and excessive build-up of FFAs are the compensatory mechanism of the cell during stress, hypoxia and high-energy consumption. FFAs as the substrate of beta-oxidation in mitochondria for production of ATP may play a compensatory rather than pathologic role, and FFA metabolism should be enhanced rather than suppressed in order to prevent and treat cancers. One compound known to have mitochondrial energy-enhancing properties is carnitine.

L-carnitine and physiological role in health and diseases

Carnitine's name is derived from the Latin word ''carnus'' or flesh, as the compound was first isolated from meat. The original discovery of carnitine occurred in 1905 when Gulewitsch and Krimberg found the substance in muscle tissue [20].

Carnitine biosynthesis occurs primarily in the liver and kidneys. The synthesis of L-carnitine is catalyzed by the concerted action of five different enzymes. This process requires two essential amino acids (lysine and methionine), iron (Fe^{2+}), vitamin C, vitamin B6 and niacin in the form of nicotinamide adenine dinucleotide (NAD) [21].

Human requirements for carnitine are usually met with a combination of diet and endogenous biosynthesis. The primary dietary sources of carnitine are meat, poultry, fish and dairy products. In comparison, vegetable products provide fairly small amounts [22]. Dietary carnitine appears to be rapidly absorbed from the intestinal lumen across the mucosal membrane by both passive and active transport mechanisms. This carnitine is then taken up from the portal circulation by the liver and subsequently released into the systemic circulation [20].

L-carnitine is a natural nutrient and essential for the beta-oxidation of fatty acids in mitochondria to generate ATP. Transport of fatty acids across this

membrane can occur only when the fatty acids are attached to carnitine. Toxic waste products resulting from energy production are removed from the mitochondria by binding to carnitine. If they are not removed, toxic build-up occurs [23,24].

Within the mitochondrial matrix, short- and medium-chain fatty acids can be transferred from CoA to L-carnitine, allowing short- and medium-chain acyl-carnitines to be exported from the mitochondria. This process provides free CoA needed for energy metabolism, as well as a mechanism to export excess acetyl and acyl groups from the mitochondria. This mechanism may also play a role in the depletion of L-carnitine during the metabolism of certain drugs [25,26].

Biosynthesis

The normal rate of L-carnitine biosynthesis in humans ranges from 0.16 to 0.48 mg/kg of body weight/day [21]. This rate of synthesis combined with the reabsorption of about 95% of the L-carnitine filtered by the kidneys is enough to prevent deficiency in generally healthy people, including strict vegetarians [22].

Carnitine deficiency

The primary carnitine deficiencies, systemic carnitine deficiency and myopathic carnitine deficiency are relatively rare hereditary disorders. Primary systemic carnitine deficiency is a genetic disorder that is usually detected in infancy or early childhood. It is characterized by low serum L-carnitine levels, and if untreated may result in life-threatening damage to the liver, heart or brain. Also known as carnitine carrier deficiency, the underlying cause is a mutation in the gene coding for the protein that transports L-carnitine into cells. As a result of this defect, intestinal absorption of dietary L-carnitine is poor and reabsorption by the kidneys is impaired, resulting in increased urinary loss of L-carnitine [21].

Primary myopathic carnitine deficiency is also a genetic disorder in which carnitine deficiency is limited to skeletal and cardiac muscle. Serum L-carnitine levels are generally normal. The symptoms of myopathic deficiency include muscle pain and progressive muscle weakness. Symptoms may begin in childhood or adulthood. The myopathic form of primary carnitine deficiency is generally less severe than the systemic form [21].

Secondary carnitine deficiencies may be hereditary or acquired. In all cases, they are characterized by decreased availability of free L-carnitine. In such cases, total L-carnitine levels may be normal, but free L-carnitine levels are decreased.

Hereditary causes of secondary carnitine deficiency include genetic defects in amino acid degradation (e.g. propionic aciduria) and lipid metabolism (e.g. medium chain acyl-CoA dehydrogenase deficiency).

Hemodialysis, Fanconi syndrome and the metabolism of some medications may result in substantial L-carnitine loss and deficiency [21].

Malabsorption syndromes and diets that chronically lack L-carnitine and its precursors may increase the risk of secondary carnitine deficiency. Premature infants may be at risk of secondary L-carnitine deficiency when fed soy-based formulas without added L-carnitine. Although dietary L-carnitine comes mainly from animal sources, even strict vegetarians can generally synthesize enough L-carnitine to prevent deficiency [22].

Possible clinical application

Aging

Age-related declines in mitochondrial function and increases in mitochondrial oxidant production are thought to be important contributors to the adverse affects of aging. Tissue L-carnitine levels have been found to decline with age in humans and animals [27]. Feeding aged rats acetyl-L-carnitine (ALCAR) reversed age-related declines in tissue L-carnitine levels and reversed a number of age-related changes in mitochondrial function, but high doses of ALCAR increased liver mitochondrial cofactors and antioxidants, improved mitochondrial energy metabolism, decreased oxidative stress and improved memory [28]. Interestingly, supplementation with the combination of ALCAR and alpha-lipoic acid (a mitochondrial protector and an energy- promoting supplement) resulted in significantly greater improvement than either compound alone [29].

During our youth, most of the body's requirements for carnitine are met by internal production of carnitine from lysine, as well as by dietary sources such as red meat and dairy products [30]. An increasing body of evidence, however, indicates that to obtain enough carnitine to secure its protective effects against aging requires supplementation in addition to dietary sources [28].

Clinical uses

Carnitine may be essential or ''conditionally essential'' for several groups of people including both children and adults suffering from a variety of genetic, infectious and injury-related illnesses. Some childhood cardiomyopathies are due to metabolic errors or deficiencies. There is data that supports treatment of some myocardial dysfunctions with L-carnitine supplementation [31]. Treatment of diseases, such as immunodeficiency virus type 1 infection/acquired immune deficiency syndrome (AIDS), may elicit or cause carnitine deficiency problems [32].

Other possible clinical applications of L-carnitine are: cardiovascular diseases [33–36]; Alzheimer's diseases and other neurodegenerative disorders [37–40]; Epilepsy [41,42]; Depression [43,44]; Physical and mental fatigues [45,46]; Pains and Neuropathies [47,48]; Maculodegeneration [49]; Diabetes and diabetic neuropathy [50–52]; Chemotherapy induced neuropathy [47,52–54]; Sexual dysfunction [55–57]; Emphysema and COPD [58]; Support for kidney failure and patients on dialysis [59–61].

Anecdotal uses of L-carnitine include: age-related cognitive decline, peripheral neuropathy (secondary to trauma), HIV infection and immune function cerebral hypoxia and ischemic reperfusion injuries, peyronie's disease, cerebral ataxia attention deficit hyperactivity disorder (ADHD), Down's syndrome, facial paralysis, male infertility, pulmonary tuberculosis, cognitive deficit due to alcoholism, chronic fatigue syndrome, amenorrhea and Parkinson's disease [62–67].

Doses, side effects and interactions

In general, L-carnitine appears to be non-toxic and well tolerated. A typical daily diet contains 5 to 100 mg of carnitine, depending on whether the diet is primarily plant-based or meat-based. Recommended supplemental doses of L-carnitine (300–2000 mg/day) vary depending on the health condition being treated. L-carnitine supplementation may cause mild gastrointestinal symptoms, including nausea, vomiting, abdominal cramps, diarrhea, increased appetite and rashes. Supplements providing more than 3000 mg/day may cause a ''fishy'' body odor [68].

Acetyl-L-carnitine has been reported to increase agitation in some Alzheimer's disease patients and to increase seizure frequency and/or severity in some individuals with seizure disorders [69]. Only the L-isomer of carnitine is biologically active. The D-isomer may actually compete with L-carnitine for absorption and transport, increasing the risk of L-carnitine deficiency [21]. Supplements containing a mixture of the D- and L-isomers (D,L-carnitine) have been associated with muscle weakness in patients with kidney disease. Controlled studies examining the safety of L-carnitine supplementation in pregnant and breast-feeding women are lacking [70].

L-carnitine and cancer

Evidences on L-carnitine anticancer activity and supportive role in cancer therapy

Low serum levels of carnitine in terminal neoplastic patients are decreased largely due to the decreased dietary intake and impaired endogenous synthesis of this substance. These low serum carnitine levels also contribute to the progression of cachexia in cancer patients [71].

L-carnitine effectively protects mitochondrial function in vivo. Pre-neoplastic lesions and hepatocarcinogenesis were significantly inhibited by L-carnitine. These facts suggest that mitochondrial injury plays an essential role in the development of hepatocarcinogenesis and that the clinical use of carnitine has excellent therapeutic potential in individuals with chronic hepatitis [72].

Studies have shown that L-carnitine can suppress colon cancer growth by reversing the blockage of mitochondrial fatty acid import in cancer cells [73].

Cachexia and carnitine

L-carnitine has been shown by various studies to benefit cancer patients with cachexia, fatigue, pain and neuropathy and chemotherapy side effects. Cancer-related anorexia/cachexia syndrome and oxidative stress play a key role in the progression and outcome of neoplastic disease. Low serum levels of carnitine in terminal neoplastic patients, which are due to a decreased dietary intake as well as to an impaired endogenous synthesis of this substance, could be an important factor in the development of cachexia in cancer patients [74].

The efficacy of L-carnitine administration has been studied in advanced cancer patients undergoing anticancer therapy. Patients on L-carnitine were noted to have an increase in lean body mass, and improvements in their fatigue and quality of life [75].

Propionyl-L-carnitine has important effects on skeletal as well as cardiac muscle. As early as 1990, human studies demonstrated that propionyl-L-carnitine could combat the destructive effects of hypoxia and muscle fatigue [76]. Several years later, it was found to contribute to the body's ability to increase muscle glycogen stores. Since glycogen is the body's most immediately available form of glucose energy storage, this may explain propionyl-L-carnitine's fatigue-reducing effects [77].

Investigators have suggested that acetyl-L-carnitine has a role in both preventing and treating chemotherapy-induced neuropathy. Moreover, these and other studies have shown that the benefits of acetyl-L-carnitine occur without diminishing the anti-cancer effects of the drugs themselves [78].

Neuro-bioenergetic role of L-carnitine in cancer prevention and management

In our prior publication, we have proposed a neuro-bioenergetic concept in cancer causation, development, prevention and treatment. The central mechanism of this concept is inducible membrane hyper-excitability via ion-gated channels, ligand-gated channels and neurotransmitters. Energy depletion, metabolism and cell cycle abnormalities, immune dysfunctions, proliferation, invasiveness, migration, cachexia and death are the results of these neuro-bioenergetic imbalances. We have suggested that using natural agents (phytochemicals, amino acids, vitamins, minerals, natural substances and other nutrients) that reduce the membrane hyper-excitability and excessive adenosine build-up, and restore cellular energy production could reverse the pathological events that can be induced by carcinogens, infections, physical and even mental stress [3,5].

Skeletal muscle catabolism, low plasma glutamine and high venous glutamate levels are common among patients with cancer or human immunodeficiency virus infection. In addition, a high glycolytic activity is commonly found in muscle tissue of cachectic cancer patients, suggesting insufficient mitochondrial energy metabolism [79].

In addition to its mitochondriotropic, energy enhancing and fatty acid metabolism modulating effects, L-carnitine may also contribute to cancer prevention and treatment by its cell membrane calming effects. Studies have indicated that L-carnitine has a modulating effect on the neurotransmitter balance of the body thus enhancing cellular differentiation. Researchers have found that acetyl-L-carnitine arginate produces rapid differentiation of immature brain cells into mature neurons, while increasing the cells' content of gamma amino-butyric acid (GABA), an important inhibitory neurotransmitter [80].

Therefore, L-carnitine may have a dual protective effect by enhancing the energy dynamics of the cell and also by inhibiting cell membrane hyperexcitability. Excitotoxic damage via upregulation of glutamate/NMDA receptors is heavily dependent on the energy state of the cell [81]. Cells with a normal energy are very resistant to such toxicity. When cells are energy deficient, no matter the cause — hypoxia, starvation, metabolic toxins or hypoglycemia, they become infinitely more susceptible to excitotoxic injury or death. Even normal concentrations of glutamate are toxic to energy deficient cells.

As we proposed in our prior hypothesis, there are similarities between neoplastic transformation and neurological morphogenesis. L-carnitine has been proven to have both strong neuroprotective activity as well as cancer preventive and therapeutic properties.

It is known that in many of the neurodegenerative disorders, neuron energy deficiency often precedes the clinical onset of the disease by years, if not decades [82]. This has been demonstrated in the case of Huntington disease and Alzheimer's disease using the PET scan, which measures brain metabolism. In the case of Parkinson's disease, several groups have demonstrated that one of the early deficits is an impaired energy in the mitochondria [83,84].

Scientific data suggest that acetyl-L-carnitine affects the function of nerve growth factor, a protein that promotes the growth and development of both central and peripheral nerve cells [85]. These mechanisms may explain how it reduces damage to brain cells caused by the amyloid beta peptide, which is found in the brains of patients with Alzheimer's disease and other neurodegenerative conditions [39,40,86].

Recently, it has been shown that when striatal neurons are exposed to microinjected excitotoxins there is a dramatic and rapid fall in energy production by these neurons. CoEnzyme Q10 has been shown, in this model, to restore energy production but not to prevent cellular death. But when combined with niacinamide, both cellular energy production and neuron protection are seen [87].

Glutamate mediated intracellular calcium accumulation and free radical generation are thought to be major mechanisms that contribute to cell death in hypoxic-ischemic brain injury. For this reason, various glutamate receptor antagonists and antioxidants have been investigated for their therapeutic

potential. L-carnitine protects against glutamate- and kainic acid-induced neurotoxicity [88].

The above review of scientific data from both clinical and basic studies shows a positive role of L-carnitine and acceptable derivatives in supportive and therapeutic roles in cancers and neurological pathologies with energy deficiencies. These mitochondrial protective and mitochondriotropic substances could help the cell reverse the inefficient energy production pattern and reverse the most prominent metabolic consequences of cancer development. Moreover, since hyper-excitability in cancer may be due to endogenous and environmental excitotoxic substances, L-carnitine could restore an optimal level of cellular energy for cellular detoxification. Ultimately, L-carnitine's improvements in metabolic function, energy and detoxification could help reverse the membrane hyper-excitability, especially in combination with other membrane calming agents.

Discussion

Cancer cells are metabolically adapted for rapid growth and proliferation under conditions of low pH and oxygen tension in which non-transformed cells would grow only poorly or not at all [89]. Of particular significance, cancer cells generate energy by glycolysis in strong preference to oxidative phosphorylation [90]. When glucose is no longer available, as can occur in solid tumors [91], cancer cells are forced to use alternative energy substrates such as the oxidation of glutamine, a process called glutaminolysis [90]. This process requires an active oxidative phosphorylation for ATP production. Under stress, the mitochondria ATP energy sources can change from fat (FFA), to glucose (glycolysis), to protein (gluconeogenesis) (Fig. 2).

In our view, the tissues and cells that become proliferative or cancerous suffer from a hyper-excitatory state of cell membrane via inducible ion-gated channels, ligand-gated channels and neurotransmitters. It is very similar to the mechanism of the development of the nervous system in embryogenesis, morphogenesis and repair during neuro-trauma. This hyper-excitatory condition can lead to depletion of cellular energy, metabolic disturbances and growth stimulation, mutagenesis, invasiveness and metastasis. In younger, healthy patients with normal nutrition, detoxification and adequate levels of ATP, the cell can eliminate excitatory factors (e.g. excitotoxins, hormones, stress, radiation) and underlying conditions (e.g. chronic infection), and the hyper-excitatory condition can be resolved. But if this neuro-bioenergetic imbalance cannot be resolved it may allow the progression of the disturbance in metabolism to progress to inflammation, dysplasia and malignancy. It is similar to the repair and healing of wounds — without the necessary energy, complete healing cannot be accomplished.

Cells must respond to environmental changes, including the availability of substrates for energy metabolism, if they are to survive. The neoplastic transformation in our view is a series of futile adaptive and compensatory cellular activities resulting from inducible neuro-bioenergetic disturbances. In our opinion, the membrane hyperexcitability produced by over-expression of voltage gated sodium channels (VGSC) and other excitatory neuronal mechanisms represent the survival strategy of the cell by the introduction of alternative means of energy production and maintenance of membrane potential and mineral homeostasis.

Normal Cells	*Early Cancer*	*Late Cancer*
Oxidation/ Phosphorylation (Glucose)	Membrane Hyperexcitability Glutamate/NMDA stimulation Glycolysis and ↑ VGSC	↑↑VGSC ↑Alternative Channels
Fatty acid B oxidation	↑ Fatty Acid Synthase/↑FFA	Glyconeogenesis
Glycolysis	↓Mitochondria Metabolism	↓↓ Mitochondria Metab.
ATP Synthesis	↓ L-Carnitine	↓↓ L-Carnitine
	↓ B-oxidation	Glutaminolysis
	↓ ATP/↑Adenosine	↓↓ATP/ ↑↑Adenosine
	↑ Toxic Build-up in Mitochondria	↑↑Toxic Build-up
		Cachexia
		Metastasis

Figure 2 Metabolic transition in cancer.

Mitochondrial Energy Enhancers	Membrane Calming Agents
L-Carnitine and derivatives	Magnesium
Fumaric Acid derivatives	PUFA
Alpha-lipoic acid	Taurine, Theanine, GABA, Glycine
PUFA	Vitamin D
Niacinamide, CoEnz Q10, Pantothenic Acid	Folic Acid
B Oxidation substrates	VGSC inhibitors/VGPC agonists
Mitochondriatropic agents	Glutamate/NMDA inhibitors
Mitochondrial protective agents	Melatonin, Progesterone

Figure 3 Mitochondrial and cell membrane agents in cancer prevention/therapy.

Researchers have proposed that there are three interchangeable energy sources, including ATP, sodium and protonic potentials, available to the living cells [92].

To help overcome a neuro-bioenergetic crisis, enhancement of mitochondrial function and effective energy production via oxidation of fatty acids by L-carnitine and acceptable derivatives may help the cells return to their normal metabolism, cycle and function (non-malignant cells). These strategies may not produce the temporary cancer shrinkages seen with traditional chemotherapy and radiation therapy, but it should improve quality of life, reduce symptoms and promote overall survival improvements without devastating side effects.

The application of L-carnitine and other possible mitochondriotropic nutrients such as alpha lipoic acid, CoEnzyme Q10, pantothenic acid and niacinamide should be of practical consideration for cancer prevention and treatments. Research on the efficacy of these agents, in combination with PUFA and membrane calming agents in cancer prevention and treatment should be pursued.

Summary

The cellular bioenergetic aspect of cancer remains an area of research that needs more attention. Currently, there are no practical recommendations regarding the rationale or advantage of any agent or intervention capable of modulating or correcting bioenergetic imbalances that are well documented in cancer patients and laboratory models of cancer. We suggest the application of non-toxic, readily available food supplements and nutriceuticals for cancer patients, such as L-carnitine and its derivatives, alpha lipoic acid, CoEnzyme Q10, pantothenic acid, niacinamide and other possible mitochondrial protectants and enhancers. As potentially effective cancer treatment and prevention, this strategy could bring even more benefit if it were combined with natural or synthetic membrane-calming agents that have been outlined in our prior publications, such as magnesium, melatonin, PUFA, folic acid, vitamin D, progesterone, theanine, VGSC and glutamate/NMDA antagonists (Fig. 3).

Conflict of Interest statement (''None declared'')

All authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence (bias) their work. We have no potential conflicts of interest which should be disclosed include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations and grants and any other funding. ''None declared''.

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