Ácido Lipóico e Câncer

01/12/2009
José de Felippe Junior

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"Nunca devemos trocar a Medicina Convencional pela Medicina Alternativa podemos sim complementar ambas com Estratégias bem estudadas da Medicina Complementar"
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"Na verdade a MEDICINA é uma só"
Vários Autores

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"Curar muitas vezes, aliviar e consolar sempre, desistir nunca"
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Amiel

Total de 17 Referências do Medline cruzando Câncer como descritor de assunto e ácido lipóico. Site: www.bireme.br

1/17

[PMID]: 17403519
[Au] Autor: Ho YS; Lai CS; Liu HI; Ho SY; Tai C; Pan MH; Wang YJ
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[Ti] Title: Dihydrolipoic acid inhibits skin tumor promotion through anti-inflammation and anti-oxidation.
[Is] ISSN: 0006-2952
[Cp] Country of publication: England
[La] Language: Eng
[Ab] Abstract: alpha-Lipoic acid (LA) has been intensely investigated as a therapeutic agent for several diseases, including hepatic disorder and diabetic polyneuropathy. However, the effects of LA or its reduced form, dihydrolipoic acid (DHLA), on cancer chemoprevention has never been reported. In the present study, we examined the effects of DHLA/LA on the production of nitric oxide (NO) by inducible NO synthase (iNOS) and the formation of prostaglandin E2 (PGE(2)) by cyclooxygenase-2 (COX-2), two important mediators associated with inflammation. DHLA/LA significantly inhibited lipopolysaccharide (LPS)-induced NO and PGE(2) formation in RAW 264.7 cells. Meanwhile, treatment with DHLA/LA suppressed the expression of iNOS protein but, unexpectedly, did not affect or increase the expression of COX-2 protein. The in vivo anti-inflammatory and antitumor-promoting activities were evaluated by a topical 12-O-tetradecanoylphorbol 13-acetate (TPA) application to mouse skin with measurement of edema formation, epidermal thickness and hydrogen peroxide production. DHLA significantly inhibited the priming and activation stages of skin inflammation induced by a double TPA application, by decreasing the inflammatory parameters. Furthermore, DHLA inhibited DMBA (0.3 micromol)/TPA (2.0 nmol)-induced skin tumor formation by reducing the tumor incidence and tumor multiplicity. When applied topically onto the shaven backs of mice prior to TPA, DHLA markedly inhibited the expression of iNOS protein. DHLA also strongly and directly inhibited COX-2 activity. These results suggest that DHLA can be a possible chemopreventive agent in inflammation-associated tumorigenesis.

2/17

[PMID]: 17136495
[Au] Autor: Simbula G; Columbano A; Ledda-Columbano GM; Sanna L; Deidda M; Diana A; Pibiri M
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Bcl-2 down-regulation. Reactive oxygen species mediate caspase activation and apoptosis induced by lipoic acid in human lung epithelial cancer cells through [Ti] Title:
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[Ad] Address:
Moungjaroen J; Nimmannit U; Callery PS; Wang L; Azad N; Lipipun V; Chanvorachote P; Rojanasakul Y

[La] Language:
Eng

[Ab] Abstract:
Alpha-lipoic acid (alpha-LA) is an antioxidant used for the treatment of a variety of diseases, including liver cirrhosis, heavy metal poisoning, and diabetic polyneuropathy. In addition to its protective effect against oxidative stress, alpha-LA induces apoptosis in different cancer cells types. However, whether alpha-LA induces apoptosis of hepatoma cells is unknown. Herein, we investigated whether alpha-LA induces apoptosis in two different hepatoma cell lines FaO and HepG2. The results showed that alpha-LA inhibits the growth of both cell lines as indicated by the reduction in cell number, the reduced expression of cyclin A and the increased levels of the Bcl-2 protein through peroxide-dependent proteasomal degradation, and overexpression of the Bcl-2 protein regulation by Bcl-2, which may be exploited for the treatment of cancer and related apoptosis disorders.

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[PMID]:
16990509

[Au] Autor:
Moungjaroen J; Nimmannit U; Callery PS; Wang L; Azad N; Lipipun V; Chanvorachote P; Rojanasakul Y

[Ad] Address:
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[Ti] Title:
Increased ROS generation and p53 activation in alpha-lipoic acid-induced apoptosis of hepatoma cells.

[So] Source:

[Is] ISSN:
0022-3565

[Cp] Country of publication:
United States

[La] Language:
Eng

[Ab] Abstract:
The antioxidant alpha-lipoic acid (LA) is a naturally occurring compound that has been shown to possess promising anticancer activity because of its ability to preferentially induce apoptosis and inhibit proliferation of cancer cells relative to normal cells. However, the molecular mechanisms underlying the apoptotic effect of LA are not well understood. We report here that LA induced reactive oxygen species (ROS) generation and a concomitant increase in apoptosis of human lung epithelial cancer H460 cells. Inhibition of ROS generation by ROS scavengers or by overexpression of antioxidant enzymes glutathione peroxidase and superoxide dismutase effectively inhibited LA-induced apoptosis, indicating the role of ROS, especially hydroperoxide and superoxide anion, in the apoptotic process. Apoptosis induced by LA was found to be mediated through the mitochondrial death pathway, which requires caspase-9 activation. Inhibition of caspase activity by the pan-caspase inhibitor (z-VAD-FMK) or caspase-9-specific inhibitor (z-LEHD-FMK) completely inhibited the apoptotic effect of LA. Likewise, the mitochondrial respiratory chain inhibitor rotenone potently inhibited the apoptotic and ROS-inducing effects of LA, supporting the role of mitochondrial ROS in LA-induced cell death. LA induced down-regulation of mitochondrial Bcl-2 protein through peroxide-dependent proteasomal degradation, and overexpression of the Bcl-2 protein prevented the apoptotic effect of LA. Together, our findings indicate a novel pro-oxidant role of LA in apoptosis induction and its regulation by Bcl-2, which may be exploited for the treatment of cancer and related apoptosis disorders.

4/17

[PMID]:
16814280

[Au] Autor:
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[Ti] Title:
Protective effect of DL-alpha-lipoic acid on cyclophosphamide induced hyperlipidemic cardiomyopathy.

[So] Source:

[Is] ISSN:
0020-4711

[Cp] Country of publication:
Netherlands

[La] Language:
Eng

[Ab] Abstract:
Cyclophosphamide is a potent alkylating agent used in cancer chemotherapy and immunosuppression. The present study is aimed at evaluating the role of a potent antioxidant lipoic acid in cyclophosphamide induced hyperlipidemic cardiomyopathy. Adult male Wistar rats were divided into four treatment groups. Two groups received single intraperitoneal injection of cyclophosphamide (200 mg/kg body weight) to induce cardiotoxicity, one of these groups received lipoic acid treatment (25 mg/kg body weight, orally for 10 days). A vehicle treated control group and a lipoic acid drug control were also included. Cyclophosphamide administration resulted in abnormal distortion in the activities of lipid metabolizing enzymes in cyclophosphamide treated group. Supplementation of lipoic acid...
reverted these abnormalities in the lipid levels and activities of lipid metabolizing enzymes to near normalcy after cyclophosphamide administration.

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[PMID]: 16574204

[Au] Author:
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[Ti] Title:
Alpha-lipoic acid modulates ovarian surface epithelial cell growth.

[So] Source:

[Is] ISSN:
0090-8258

[Cp] Country of publication:
United States

[La] Language:
Eng

[Ab] Abstract:
OBJECTIVE: The intracellular redox state plays an important role in controlling inflammation. Clinical and laboratory data suggest that inflammation can lead to tumor progression. We hypothesized that restoring intracellular redox control would inhibit inflammation and subsequently tumor progression. Our studies were designed to investigate the effect of alpha-lipoic acid (ALA), a naturally occurring antioxidant, on a key inflammatory signaling pathway and cell proliferation in normal and tumorigenic ovarian surface epithelial cells.

METHODS: Normal and tumorigenic ovarian surface epithelial cells were isolated as described by Roby and coworkers [Roby KF, Taylor CC, Sweetwood JP, Cheng Y, Pace JL, Tawpik O, Persons DL, Smith PG, Terranova PF, Development of a syngeneic mouse model for events related to ovarian cancer. Carcinogen 2000;21 (4):585. [1]]; the effect of ALA on cellular function was measured in cell proliferation and apoptosis assays. p27(kip1) protein levels were measured by Western analysis. Activation of NF-kappaB dependent transcription was assessed in cell cultures transiently transfected with NF-kappaB controlled reporter constructs. RESULTS: Our results reveal that ALA selectively inhibits the growth of tumorigenic as compared to non-tumorigenic ovarian surface epithelial cells. The growth inhibitory effect of ALA is not due to induction of apoptosis but instead is associated with an increase in the half-life of the cyclin-dependent kinase inhibitor, p27(kip1). In parallel to the growth inhibitory effect, ALA also affects a key inflammatory signaling pathway by inhibiting TNF-alpha-induced NF-kappaB signaling activity. CONCLUSIONS: Our studies are the first to show that ALA treatment has a growth inhibitory effect on malignant surface epithelial cells of ovarian origin. We have also confirmed the reproducibility of the immunocompetent mouse ovarian cancer model originally described by Roby and coworkers [Roby KF, Taylor CC, Sweetwood JP, Cheng Y, Pace JL, Tawpik O, Persons DL, Smith PG, Terranova PF, Development of a syngeneic mouse model for events related to ovarian cancer. Carcinogen 2000;21 (4):585].

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PMID:
167072588

[Au] Author:
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[Ti] Title:
A phase II study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress.

[So] Source:

[Is] ISSN:
1055-9965

[La] Language:
Eng

[Ab] Abstract:
PURPOSE: To test the efficacy and safety of an integrated treatment based on a pharmaconutritional support, antioxidants, and drugs, all given orally, in a population of advanced cancer patients with cancer-related anorexia/cachexia and oxidative stress. Patients and METHODS: An open early-phase II study was designed according to the Simon two-stage design. The integrated treatment consisted of diet with high polyphenols content (400 mg), antioxidant treatment (300 mg/d alpha-lipoic acid + 2.7 g/d carbocysteine lysine salt + 400 mg/d vitamin E + 30,000 IU/d vitamin A + 500 mg/d vitamin C), and pharmaconutritional support enriched with 2 cans per day (n-3)-PUFA (ecosapentaenoic acid and docosahexaenoic acid), 500 mg/d medroxyprogesterone acetate, and 200 mg/d selective cyclooxygenase-2 inhibitor celecoxib. The treatment duration was 4 months. The following variables were evaluated: (a) clinical (Eastern Cooperative Oncology Group performance status); (b) nutritional [lean body mass (LBW), appetite, and resting energy expenditure]; (c) laboratory [proinflammatory cytokines and leptin, reactive oxygen species (ROS) and antioxidant enzymes]; (d) quality of life (European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D, and MFSI-SF). RESULTS: From July 2002 to January 2005, 44 patients were enrolled. Of these, 39 completed the treatment and were assessable. Body weight increased significantly from baseline as did LBW and appetite. There was an important decrease of proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha, and a negative relationship worthy of note was only found between LBW and IL-6 changes. As for quality of life evaluation, there was a marked improvement in the European Organization for Research and Treatment of Cancer QLQ-C30, Euro QL-5D(VAS), and multidimensional fatigue symptom inventory-short form scores. At the end of the study, 22 of the 39 patients were [quote ]responders[quote ] or [quote ]high responders[quote ]; the minimum required was 21; therefore, the treatment was effective and more importantly was shown to be safe. CONCLUSION: The efficacy and safety of the treatment have been shown by the study; therefore, a randomized phase III study is warranted.
Integrative Medical Center of New Mexico and New Mexico State University, Las Cruces.

**[Ti]** Title: The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol.


**[Is]** ISSN: 1534-7354

**[Cp]** Country of publication: United States

**[La]** Language: Eng

**[Ab]** Abstract: The authors describe the long-term survival of a patient with pancreatic cancer without any toxic adverse effects. The treatment regimen includes the intravenous alpha-lipoic acid and low-dose naltrexone (ALA-N) protocol and a healthy lifestyle program. The patient was told by a reputable university oncology center in October 2002 that there was little hope for his survival. Today, January 2006, however, he is back at work, free from symptoms, and without appreciable progression of his malignancy. The integrative protocol described in this article may have the possibility of extending the life of a patient who would be customarily considered to be terminal. The authors believe that life scientists will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological platform. But until such protocols come to market, the ALA-N protocol should be studied and considered, given its lack of toxicity at levels reported. Several other patients are on this treatment protocol and appear to be doing well at this time.

8/17

**[PMID]**: 15843897

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**[Ti]** Title: alpha-Lipoic acid induces apoptosis in human colon cancer cells by increasing mitochondrial respiration with a concomitant O2-·-generation.


**[Is]** ISSN: 1360-8185

**[Cp]** Country of publication: United States

**[La]** Language: eng

**[Ab]** Abstract: The antioxidant alpha-lipoic acid (ALA) has been shown to affect a variety of biological processes associated with oxidative stress including cancer. We determined in HT-29 human colon cancer cells whether ALA is able to affect apoptosis, as an important parameter disregulated in tumour development. Exposure of cells to ALA or its reduced form dihydrolipoic acid (DHLA) for 24 h dose dependently increased caspase-3-like activity and was associated with DNA-fragmentation. DHLA but not ALA was able to scavenge cytosolic O2-· in HT-29 cells whereas both compounds increased O2-·-generation inside mitochondria. Increased mitochondrial O2-·-production was preceded by an increased influx of lactate or pyruvate into mitochondria and resulted in the down-regulation of the anti-apoptotic protein bcl-X(L). Mitochondrial O2-·-generation and apoptosis induced by ALA and DHLA could be prevented by the O2-·-scavenger benzoquinone. Moreover, when the lactate/pyruvate transporter was inhibited by S-nitro-2-(3-phenylpropy)amine) benzoate, ALA- and DHLA-induced mitochondrial ROS-production and apoptosis were blocked. In contrast to HT-29 cells, no apoptosis was observed in non-transformed human colonocytes in response to ALA or DHLA addition. In conclusion, our study provides evidence that ALA and DHLA can effectively induce apoptosis in human colon cancer cells by a prooxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria.

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**[PMID]**: 11896744

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**[Ti]** Title: Sulfur in human nutrition and applications in medicine.


**[Is]** ISSN: 1089-5159

**[Cp]** Country of publication: United States

**[La]** Language: eng

**[Ab]** Abstract: Because the role of elemental sulfur in human nutrition has not been studied extensively, it is the purpose of this article to emphasize the importance of this element in humans and discuss the therapeutic applications of sulfur compounds in medicine. Sulfur is the sixth most abundant macrominerals in breast milk and the third most abundant mineral based on percentage of total body weight. The sulfur-containing amino acids (SAAs) are methionine, cysteine, cystine, homocysteine, homocystine, and taurine. Dietary SAA analysis and protein supplementation may be indicated for vegan athletes, children, or patients with HIV, because of an increased risk for SAA deficiency in these groups. Methylsulfonylmethane (MSM), a volatile component in the sulfur cycle, is another source of sulfur found in non-transformed human colonocytes in response to ALA or DHLA addition. In conclusion, our study provides evidence that ALA and DHLA can effectively induce apoptosis in human colon cancer cells by a prooxidant mechanism that is initiated by an increased uptake of oxidizable substrates into mitochondria.
discussed. The low toxicological profiles of these sulfur compounds, combined with promising therapeutic effects, warrant continued human clinical trials.

10/17

[PMID]: 11384106

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[Ad] Address: Bio-Communications Research Institute, Center for the Improvement of Human Functioning International, 3100 North Hillside Avenue, Wichita, KS 67219, USA.

[Ti] Title: Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours.


[Is] ISSN: 0007-0920

[La] Language: eng

[Ab] Abstract: Vitamin C (ascorbate) is toxic to tumour cells, and has been suggested as an adjuvant cancer treatment. Our goal was to determine if ascorbate, in combination with other antioxidants, could kill cells in the SW620 hollow fibre in vitro solid tumour model at clinically achievable concentrations. Ascorbate anti-cancer efficacy, alone or in combination with lipoic acid, vitamin K3, phenyl ascorbate, or doxorubicin, was assessed using annexin V staining and standard survival assays. 2-day treatments with 10 mM ascorbate increased the percentage of apoptotic cells in SW620 hollow fibre tumours. Lipoic acid synergistically enhanced ascorbate cytotoxicity, reducing the 2-day LC(50) in hollow fibre tumours from 34 mM to 4 mM. Lipoic acid, unlike ascorbate, was equally effective against proliferating and non-proliferating cells. Ascorbate levels in human blood plasma were measured during and after intravenous ascorbate infusions. Infusions of 60 g produced peak plasma concentrations exceeding 20 mM with an area under the curve (24 h) of 76 mM h. Thus, tumoricidal concentrations may be achievable in vivo. Ascorbate efficacy was enhanced in an additive fashion by phenyl ascorbate or vitamin K3. The effect of ascorbate on doxorubicin efficacy was concentration dependent; low doses were protective while high doses increased cell killing.

11/17

[PMID]: 10842199

[Au] Autor: Mantovani G; Macciò A; Melis G; Mura L; Massa E; Mudu MC

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[Ti] Title: Restoration of functional defects in peripheral blood mononuclear cells isolated from cancer patients by thiol antioxidants alpha-lipoic acid and N-acetyl cysteine.


[Is] ISSN: 0020-7136

[La] Language: eng

[Ab] Abstract: The ability of Alpha-Lipoic Acid (ALA) and N-Acetyl Cysteine (NAC), two active antioxidant agents, to correct in vitro the most significant functional defects of peripheral blood mononuclear cells (PBMC) isolated from advanced stage cancer patients was studied. The proliferative response of PBMC isolated from cancer patients to anti-CD3 monoclonal antibody (MAb) and the expression of CD25 (IL-2R) and CD95 (Fas) on unstimulated and anti-CD3 MAb-stimulated PBMC were studied, and the serum levels of proinflammatory cytokines IL-1, IL-6, TNFalpha as markers of pro-cachectic activity in cancer patients, and the serum levels of IL-2 and sIL-2R were assessed. Twenty patients (mean age 64.6 years) with cancer of lung, ovary, endometrium, and head and neck, all in advanced (III, IV) stage of disease, were studied. The serum levels of IL-1beta, IL-2, IL-6, TNFalpha, and sIL-2R were significantly higher in cancer patients than in normal subjects. The response of PBMC isolated from cancer patients to anti-CD3 MAB was significantly lower than that of controls. The addition of either ALA 0.001 mM or NAC 0.004 mM in the PBMC cultures stimulated with anti-CD3 MAB significantly increased the response of PBMC isolated from cancer patients and normal subjects. After 24 and 72 hr of culture with anti-CD3 MAB, the expression of CD25 and CD95 on PBMC isolated from cancer patients was significantly lower than that of PBMC isolated from normal subjects. The addition of either ALA or NAC into cultures of PBMC isolated from cancer patients significantly increased the percentage of cells expressing CD25 as well as those expressing CD95. The results of the present study show a favorable effect of antioxidant agents ALA and NAC on several important T-cell functions in vitro in advanced-stage cancer patients.

12/17

[PMID]: 9305611

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[Ti] Title: Induction of the differentiation of HL-60 promyelocytic leukemia cells by vitamin E and other antioxidants in combination with low levels of vitamin D3: possible relationship to NF-kappaB.


[Is] ISSN: 0887-6924

[La] Language: eng

[Ab] Abstract: The ability of Alpha-Lipoic Acid (ALA) and N-Acetyl Cysteine (NAC), two active antioxidant agents, to correct in vitro the most significant functional defects of peripheral blood mononuclear cells (PBMC) isolated from advanced stage cancer patients was studied. The proliferative response of PBMC isolated from cancer patients to anti-CD3 monoclonal antibody (MAb) and the expression of CD25 (IL-2R) and CD95 (Fas) on unstimulated and anti-CD3 MAb-stimulated PBMC were studied, and the serum levels of proinflammatory cytokines IL-1, IL-6, TNFalpha as markers of pro-cachectic activity in cancer patients, and the serum levels of IL-2 and sIL-2R were assessed. Twenty patients (mean age 64.6 years) with cancer of lung, ovary, endometrium, and head and neck, all in advanced (III, IV) stage of disease, were studied. The serum levels of IL-1beta, IL-2, IL-6, TNFalpha, and sIL-2R were significantly higher in cancer patients than in normal subjects. The response of PBMC isolated from cancer patients to anti-CD3 MAB was significantly lower than that of controls. The addition of either ALA 0.001 mM or NAC 0.004 mM in the PBMC cultures stimulated with anti-CD3 MAB significantly increased the response of PBMC isolated from cancer patients and normal subjects. After 24 and 72 hr of culture with anti-CD3 MAB, the expression of CD25 and CD95 on PBMC isolated from cancer patients was significantly lower than that of PBMC isolated from normal subjects. The addition of either ALA or NAC into cultures of PBMC isolated from cancer patients significantly increased the percentage of cells expressing CD25 as well as those expressing CD95. The results of the present study show a favorable effect of antioxidant agents ALA and NAC on several important T-cell functions in vitro in advanced-stage cancer patients.
ENGLAND

[La] Language: eng

[Ab] Abstract:
Epidemiological studies have provided evidence that diets rich in antioxidant nutrients may reduce the risk of cancer. To evaluate the possibility that dietary phytochemicals with antioxidant potential would create an environment capable of affecting the differentiation of HL-60 leukemia cells, we measured the effects of vitamin E and other dietary antioxidants on the differentiation produced by low levels of vitamin D3 and analogs thereof. Vitamin E succinate and other antioxidant compounds (ie butylated hydroxyanisole, beta-carotene and lipoic acid) used alone had no significant effect on the differentiation of HL-60 cells; however, these agents markedly increased the differentiation produced by vitamin D3. Previous studies from this laboratory have shown that a sequence-specific antisense phosphorothioate oligonucleotide to the Rel A subunit of NF-kappaB enhanced the differentiation of HL-60 cells produced by several inducing agents. Consistent with these observations, vitamin E succinate caused a marked reduction in the nuclear content of NF-kappaB both in the presence and absence of vitamin D3. These findings suggest that NF-kappaB may be a factor in regulating the differentiation of myeloid leukemia cells. The results also indicate that combinations of vitamin D3 and analogs thereof with dietary antioxidants may be useful in overcoming the differentiation block present in acute promyelocytic leukemia cells.

13/17

[PMID]: 9290147

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[Ti] Title:
Characterization of a sodium-dependent vitamin transporter mediating the uptake of pantothenate, biotin and lipoate in human placental choriocarcinoma cells.

[S0] Source:

[Is] ISSN:
0143-4004

[Cp] Country of publication:
ENGLAND

[La] Language: eng

[Ab] Abstract:
The characteristics of the uptake of the vitamin pantothenate into JAr human placental choriocarcinoma cells were investigated and these cells were found to accumulate the vitamin against a concentration gradient by a Na(+)-dependent process. Substitution of Na+ with other monovalent cations abolished the uptake completely. The transport process showed no preference for any particular anion. Kinetic analysis indicated the presence of a single saturable transport system with a Michaelis-Menten constant of 2.1 +/- 0.2 microM and a maximal velocity of 341 +/- 12 pmol/mg of protein per 10 min. The dependence of the uptake rate of pantothenate on Na+ concentration exhibited sigmoidal kinetics, indicating interaction of more than one Na+ ion with the transporter. The Hill coefficient for this process was calculated to be 1.6. The Na+/pantothenate coupling ratio being greater than unity suggests that the transport process is electrogenic, resulting in net transfer of positive charge across the membrane. This was confirmed in plasma membrane vesicles prepared from JAr cells where the uptake of pantothenate was found to be significantly stimulated by valinomycin-induced inside-negative K(+)-diffusion potential. Substrate specificity studies showed that, in addition to pantothenate, the transporter interacts with two other vitamins, namely biotin and lipoate. The characteristics of pantothenate uptake in the placental cell line BeWo was also investigated. These cells were also found to express a pantothenate transport system similar to that expressed in the JAr cells.

14/17

[PMID]: 7669066

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[Ad] Address:
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[Ti] Title:
Interaction of alpha-lipoic acid enantiomers and homologues with the enzyme components of the mammalian pyruvate dehydrogenase complex.

[S0] Source:

[Is] ISSN:
0006-2952

[Cp] Country of publication:
ENGLAND

[La] Language: eng

[Ab] Abstract:
Lipoic acid (alpha-lipoic acid, thiotic acid) is applied as a therapeutic agent in various diseases accompanied by polynuropathia such as diabetes mellitus. The stereoselectivity and specificity of lipoic acid for the pyruvate dehydrogenase complex and its component enzymes from different sources has been studied. The dihydrolipoamide dehydrogenase component from pig heart has a clear preference for R-lipoic acid, a substrate which reacts 24 times faster than the S-enantiomer. Selectivity is more at the stage of the catalytic reaction than of binding. The Michaels constants of both enantiomers are comparable (Km = 3.7 and 5.5 mM for R- and S-lipoic acid, respectively) and the S-enantiomer inhibits the R-lipoic acid dependent reaction with an inhibition constant similar to its Michaels constant. When three lipoic acid homologues were tested, RS-1,2-dithiolane-3-carboxic acid was one carbon atom longer than lipoic acid, while RS-bisnorlipoic acid and RS-tetranorlipoic acid were two and four carbon atoms shorter, respectively. All are poor substrates but bind to and inhibit the enzyme with an affinity similar to that of S-lipoic acid. No essential differences with respect to its reaction with lipoic acid enantiomers and homologues exist between free and complex-bound dihydrolipoamide dehydrogenase. Dihydrolipoamide dehydrogenase from human renal carcinoma has a higher Michaels constant for R-lipoic acid (Km = 18 mM) and does not accept the S-enantiomer as a substrate. Both enantiomers of lipoic acid are inhibitors of the overall reaction of the bovine pyruvate dehydrogenase complex, but stimulate the respective enzyme complexes from rat as well as from Escherichia coli. The S-enantiomer is the stronger inhibitor, the R-enantiomer the better activator. The two enantiomers have no influence on the partial reaction of the bovine pyruvate dehydrogenase component, but do inhibit the enzyme component from rat kidney. The implications of these results are discussed.

15/17

http://www.medicinacomplementar.com.br/convertido/ca-0458.htm

Department of Toxicology, Oncology and Molecular Pathology Unit, Italy.

Alpha-lipoic acid (alpha-LA) is an antioxidant used for the treatment of a variety of diseases, including liver cirrhosis, heavy metal poisoning, and diabetic polyneuropathy. In addition to its protective effect against oxidative stress, alpha-LA induces apoptosis in different cancer cells types. However, whether alpha-LA induces apoptosis of hepatoma cells is unknown. Herein, we investigated whether alpha-LA induces apoptosis in two different hepatoma cell lines FaO and HepG2. The results showed that alpha-LA inhibits the growth of both cell lines as indicated by the reduction in cell number, the reduced expression of cyclin A and the increased levels of the cyclin/CDKs inhibitors, p27(Kip1) and p21(Cip1). Cell cycle arrest was associated with cell loss, and DNA laddering indicative of apoptosis. Apoptosis was preceded by increased generation of reactive oxygen species, and associated with p53 activation, increased expression of Bax, release of cytochrome c from mitochondria, caspases activation, decreased levels of survivin, induction of pro-apoptotic signaling (i.e JNK) and inhibition of anti-apoptotic signaling (i.e PKB/Akt) pathways. In conclusion, this study provides evidence that alpha-LA induces apoptosis in hepatoma cells, describes a possible sequence of molecular events underlying its lethal effect, and suggests that it may prove useful in liver cancer therapy.

PMID: 17136495