Support Regimen for Multiple Sclerosis

Diet: Paleolithic ("Stone Age"). 30% or more protein (2:1 ratio of omega-3 to omega-6 fatty acid containing fish, game meat, etc., 1:1 Magnesium to Calcium intake, low sodium-high potassium) 70% complex carbohydrates (Fruits and vegetables**).** No grains, cereals or bovine milk. (Helpful dietary chart can be found further down below)

Use of curry and Tumeric powder in foods is encouraged.

Dissolve one lozenge orally before, during or after meals

Pregnenolone 10 mgs **(Maximum 3 daily)**

One with Breakfast and one with lunch

1.5 grams time-released **Niacinamide**

20 minutes before or 1 hour after meals:

1 gram (1000 mgs) of **Acetyl-L-carnitine**

500 mgs. to 1 gram (1000 mgs): **Taurine**

With meals:

1 **Cinnamon Extract (20:1) Capsule**

100 mgs. **R-Lipoic Acid**

Drink magnesium rich "hard" water as often as possible: http://www.mgwater.com/list5.shtml . Also make green tea using this type of water (See below)

Make and drink organic Japanese green tea 2-3 times daily http://www.o-cha.com/green-tea/organic-matcha-supreme.html -. This is one of the best, **"Kaoru Supreme"** Make using a magnesium rich water (See above for one source). **NOTE: Author has no financial or other interest in this firm or any commercial source listed in this regimen.**

Rooibos Tea (Rich in luteolin):

http://www.dragonwater.com/search.tf/tea/rooibos_tea/?z=go_rooibos_tea&gclid=CKq9g-rR6IMCFQMZIgodqzqpLw - Organic Rooibos Tea

T4 (Thyroid) – Check with primary care physician regarding advisability of using this (MD or DO must monitor T4 hormone level regularly). Abstract concerning rationale for inclusion in references section.

At Bedtime (Check with physician – Rx item)

4.5-5 mgs. **Naltrexone**

http://www.lowdosenaltrexone.org/ldn_and_ms.htm

Blue Spectrum Light

http://www.amazon.com/Philips-GoLite-Spectrum-Therapy-Device/dp/B000C1946S

Dietary Chart

70 % Per Day	30% Per Day **(Especially the high Protein Meats & such)**	0% Per Day
Chlorophyll foods	Jerusalem Artichoke	Cigarettes/Cigars
Chlorella	Avocado	
Sprouts	Brussel Sprouts	Beer
Asparagus	Broccoli	Wine
Beets	Eggplant	Other Alcoholic drinks
	Carrots	Sodas
Carob	Carrot Juice (no more than ½ glass)	Coffee (Caffeinated)
Cauliflower	Blueberries	
Celery	Red Grapes	Red Meat
Chard	Grape Juice	
Cucumber	Onions, garlic	**All grains and cereals**
Green beans	Wheat grass juice	
Kale		
Leafy lettuce		Cloves
Mustard greens	Almonds and filberts (not roasted or salted)	
Parsnips	Sunflower seeds	Foods with
Prunes (bedtime)	Sesame seeds	Artificial colors
Radishes	Pumpkin seeds	Preservatives
Spinach	Olives	Monosodium glutamate or Vegetable Hydrolyzed Protein
String beans		
Sweet potatoes		

Watercress

Vegetable Juices

(Green and Yellow)

Curcumin/Curry

Cinnamon

Ginger

Ginseng

Fenugreek

Rosemary

Parsley/Cilantro

Sage

Thyme

Natural vanilla flavoring

Knox Gelatin

Fish (be careful of mercury content)

Cod

Haddock

Flounder

Salmon

Scrod

Tuna

Sea Bass

Bass

Sardines

Herring

Anchovies

Turkey

Chicken

Eggs

Wild Game

Processed foods with increased salt or sugar

Aspartame (Nutrasweet)

Fried Foods

Water with heavy metals

(fluoride water can increase the toxicity of aluminum)

Dairy Products

Sweeten foods and beverages with Trehalose

One source for Trehalose: http://www.endowmentmed.org/content/view/902/122/

Resources, References, Supporting Material

http://author.emedicine.com/NEURO/topic286.htm - Organophosphates, general.

http://www.safe2use.com/ca-ipm/00-11-12.htm - The Chronic and Delayed Effects of Organophosphate (OP) Poisoning

http://www.webnat.com/ - Neurodegenerative diseases and conditions: Causes, natural and other treatments, et cetera

Diet, supplements, abstracts, etc.

Tumeric (Curcumin)

Curcumin (Diferuloylmethane) is a compound found in the Indian curry spice, **tumeric**.

It has been discovered that people in India have a very low incidence of neurological diseases and researchers have attempted to find out why this is. They have looked at the spice, **tumeric**, which was known from traditional Indian medicine as an anti-inflammatory agent effective in wound healing. Research using curcumin, the active ingredient of tumeric, in EAE, a mouse model of multiple sclerosis, has shown that it may be of benefit to people with MS.

Curry spice may fight multiple sclerosis
The Spice of Life - Unlocking the power of curcumin
Piperin Home page
Curcuma longa (turmeric). Monograph.
Curcumin inhibiting of TNF-mediated adhesion of monocytes to endothelial cells
Curcumin inhibiting of macrophage TNF-alpha release
Effect of curcumin and capsaicin on rat macrophages metabolism
Curcumin inhibiting differentiation in human endothelial cells
Curcumin and oxidative activity astrocyte cells
Regulation of IL-1 mediated MMP-9 expression in mesangial cells
Influence of piperine on curcumin in animals and humans
Immunomodulatory activity of curcumin

J Immunol. 2002 Jun 15;168(12):6506-13.

Curcumin inhibits experimental allergic encephalomyelitis by blocking IL-12 signaling through

Janus kinase-STAT pathway in T lymphocytes.

Natarajan C, Bright JJ.

Division of Neuroimmunology, Department of Neurology, Vanderbilt University Medical Center, Nashville, TN 37212, USA.

Experimental allergic encephalomyelitis (EAE) is a CD4(+) Th1 cell-mediated inflammatory demyelinating autoimmune disease of the CNS that serves as an animal model for multiple sclerosis (MS). IL-12 is a proinflammatory cytokine that plays a crucial role in the induction of neural Ag-specific Th1 differentiation and pathogenesis of CNS demyelination in EAE and MS. Curcumin (1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a naturally occurring polyphenolic phytochemical isolated from the rhizome of the medicinal plant Curcuma longa. It has profound anti-inflammatory activity and been traditionally used to treat inflammatory disorders. In this study we have examined the effect and mechanism of action of curcumin on the pathogenesis of CNS demyelination in EAE. In vivo treatment of SJL/J mice with curcumin significantly reduced the duration and clinical severity of active immunization and adoptive transfer EAE. Curcumin inhibited EAE in association with a decrease in IL-12 production from macrophage/microglial cells and differentiation of neural Ag-specific Th1 cells. In vitro treatment of activated T cells with curcumin inhibited IL-12-induced tyrosine phosphorylation of Janus kinase 2, tyrosine kinase 2, and STAT3 and STAT4 transcription factors. The inhibition of Janus kinase-STAT pathway by curcumin resulted in a decrease in IL-12-induced T cell proliferation and Th1 differentiation. These findings highlight the fact that curcumin inhibits EAE by blocking IL-12 signaling in T cells and suggest its use in the treatment of MS and other Th1 cell-mediated inflammatory diseases.

PMID: 12055272 [PubMed - indexed for MEDLINE]

NEW ORLEANS (Reuters Health) - **Preliminary studies in rats suggest that curcumin, a compound found in the curry spice turmeric, may block the progression of multiple sclerosis (MS).**

According to researcher Dr. Chandramohan Natarajan of Vanderbilt University in Nashville, Tennessee, rats with an MS-like illness showed little or no signs of disease symptoms after being injected with curcumin, while animals without the treatment went on to severe paralysis.

"We got a very good inhibition of the disease by treating with curcumin," Natarajan told Reuters Health. He presented the findings here Tuesday at the annual Experimental Biology 2002 conference.

No one knows what causes multiple sclerosis, in which the body's immune system attacks the protective myelin sheath surrounding nerve fibers in the brain and spine. Symptoms of multiple sclerosis include muscle weakness and stiffness, balance and coordination problems, numbness and vision disturbances.

Interest in the potential neuroprotective properties of curcumin rose after studies found very low levels of neurological diseases

such as Alzheimer's in elderly Indian populations. Added to this were studies confirming curcumin as a potent anti-inflammatory agent, effective in wound healing. And just last fall, researchers at the University of California, Los Angeles reported that curcumin appeared to slow the progression of Alzheimer's in mice.

In their 30-day study, Natarajan and co-researcher Dr. John Bright gave injections of 50- and 100-microgram doses of curcumin, three times per week, to a group of mice bred to develop a disease called experimental autoimmune encephalomyelitis (EAE)--an autoimmune condition used by researchers as a model for multiple sclerosis because it also results in the slow erosion of myelin. They then watched the rats for signs of MS-like neurological impairment.

By day 15, rats who had not received curcumin developed EAE to such an extent that they displayed complete paralysis of both hind limbs, according to Natarajan.

In contrast, rats given the 50-microgram dose of the curry compound showed only minor symptoms, such as a temporarily stiff tail. And rats given the 100-microgram dose appeared completely unimpaired throughout the 30 days of the study.

The results didn't really surprise Natarajan. "In Asian countries, such as India, China, who are eating more spicy foods, more yellow compounds like curcumin...there are only very, very rare reports of MS," he pointed out. He said the doses the rats received were roughly equivalent in human terms to those found in a typical Indian diet.

Just how curcumin might work to thwart the progression of demyelinization remains unclear. But the Nashville researchers believe it may interrupt the production of IL-12, a protein that plays a key role in signaling immune cells to launch their assault on the myelin sheath.

Natarajan stressed that "we have to do a lot of work on this," including examining other potential mechanisms by which curcumin slows EAE and, potentially, MS.

The work remains preliminary, and MS patients should follow their doctor's advice when it comes to treating the disease. Still, Natarajan said adding a little curry to the diet couldn't hurt. "I think using this spice in their food could be of help," he said.

http://www.iherb.com/tumeric.html

Blue Wavelength light exposure may ameliorate MS

Animal Model of Multiple Sclerosis:

• To help in research of multiple sclerosis (MS) researchers utilize an animal model, experimental allergic encephalitis (EAE). EAE is an acute autoimmune demyelination disease, that matches the symptomatology of MS. Guinea pigs with EAE are reported to have a reduction of serotonin within the central nervous system (CNS), when compared to control subjects. The reduction of serotonin within the CNS leads to an effect on CNS serotonin transmissions in EAE, either at the level of serotonin receptor itself, or at the level of serotonin transmitting neurons (Scott, Cashman, and Spitler, 1982-83). The symptoms of EAE are due to the inhibition of serotonin transmission.

In animals with EAE, administration of L-5-hydroxytrytophan, a precursor to serotonin, reversed the effects of impaired serotonergic transmission. Suggesting that there might be a blockade of serotonin receptors (Scott, Cashman, and Spitler, 1982-83), which can be overcome by the addition of a drug that increases the CNS serotonin levels. The addition of a precursor of serotonin has such an effect, and then the addition of antidepressant type drugs may affect the symptoms of EAE in a positive way. ・/SPAN>

http://www.cwu.edu/~chem/courses/chem388488f00/kusche/multiple/animal.htm

---

Scientific Breakthrough Blue Light Wavelengths Increase Serotonin

Several very recent studies, most notably research from a team headed by Dr. George Brainard at Thomas Jefferson Medical College in Philadelphia, have identified the specific wavelengths of **blue light, 446-477 nm that are crucial in suppressing melatonin production in humans**. [1] [2] [3] [4] As Dr. Brainard notes, "This discovery will have an immediate impact on the therapeutic use of light for treating winter depression and circadian disorders." Melatonin, the neurotransmitter that helps us sleep deeply through the night, is produced from serotonin. Suppressing melatonin production raises the levels of serotonin in our brains. This is the key goal of therapeutic bright light treatment. This neurological pathway entrains our circadian rhythm to be awake during the day and sleep deeply at night.

Four cells in the human retina capture light and form the visual system. One type, rod cells, regulates night vision. The other three types, called cone cells, control color vision. It's known that exposure to light at night can disrupt the body's production of melatonin, which is produced by the pineal gland in the brain and plays a vital role in resetting the body's daily biological clock.

Dr. Brainard and his group showed that the combined three-cone system didn't control the biological effects of light, at least not for melatonin regulation. But subsequent work led to the surprising discovery that a novel receptor was responsible for the effect.

The study looked at the effects of nine different wavelengths of light, from indigo to orange, on 72 healthy volunteers. Subjects were brought into the laboratory at midnight, when melatonin is highest. The subjects' pupils were dilated and then they were blindfolded for two hours. Blood samples were drawn. Next, each person was exposed to a specific dose of photons of one light for 90 minutes, and then another blood sample was drawn. Wavelengths of **blue light had the highest potency in causing changes in melatonin levels,** he explains.

This new research indicates that there is an as yet unidentified photopigment; most sensitive at theses wavelengths of blue light that controls theses neurological reactions to light. As another researcher notes, this 'provides the first direct evidence of a non-rod, non-cone photoreceptive system in humans' - one that is activated by blue light between 420-480 nm. [2]

We are pleased to announce that this research has been incorporated into the BlueStarTM Light Boxes. The 10 000 lux, BlueStarTM double tubes have one side that's bright blue (446-477 nm) and one side that's bright white 85 CRI, 5000K. Clinical use shows that the BlueStarTM Light raises serotonin in 15-30 minutes, instead of the 1-2 hours necessary with bright hi lux light

1. Brainard G, Hanifin J, Gresson J, et al (2001) Action Spectrum for Melatonin Regulation in Humans: Evidence for a Novel Circadian Photoreceptor. Neurosci (16):

6405-6412
2 Thapan K, Arendt J, Skene DJ (2001) An action spectrum for melatonin suppression: evidence for a novel non-rod, non-cone photoreceptor system in humans. J Physiol 535 (pt 1): 261-7
3 Wright HR, Lack LC (2001) Effect of light wavelength on suppression and phase delay of the melatonin rhythm. Chronobiol Int 5:801-8

4 Max, M (2001) Molecular Basis of Phototransduction and Circadian Rhythmicity, notes on current research, Dept. of

Physiology and Biophysics of Mount Sinai School of Medicine.

NIACINAMIDE (Nerve protectant and anti-inflammatory)

Clin Exp Immunol. 2003 Jan;131(1):48-52.

Nicotinamide is a potent inhibitor of proinflammatory cytokines.

Ungerstedt JS, Blomback M, Soderstrom T.

Coagulation Research, Department of Surgical Sciences, Karolinska Institutet, Stockholm, Sweden.
johanna.ungerstedt@ks.se

The present study investigates the modulating effects of nicotinamide on the cytokine response to endotoxin. In an in vitro model of endotoxaemia, human whole blood was stimulated for two hours with endotoxin at 1 ng/ml, achieving high levels of the proinflammatory cytokines IL-1 beta, IL-6, IL-8 and TNF alpha. When coincubating whole blood, endotoxin and the vitamin B3 derivative nicotinamide, all four cytokines measured were inhibited in a dose dependent manner. Inhibition was observed already at a nicotinamide concentration of 2 mmol/l. At a concentration of 40 mmol/l, the IL-1 beta, IL-6 and TNF alpha responses were reduced by more than 95% and the IL-8 levels reduced by 85%. Endotoxin stimulation activates poly(ADP-ribose)polymerase (PARP), a nuclear DNA repair enzyme. It has been hypothesized that the anti-inflammatory properties of nicotinamide are due to PARP inhibition. In the present study, the endotoxin induced PARP activation was dose dependently decreased with 4-40 mmol/l nicotinamide or 4-100 micro mol/l 6(5H) phenanthridinone, a specific PARP inhibitor. 6(5H)phenanthridinone however, failed to inhibit the proinflammatory cytokines. Thus, the mechanism behind the cytokine inhibition in our model seems not to be due to PARP inhibition. In conclusion, the present study could not only confirm previous reports of a down-regulatory effect on TNFalpha, **but demonstrates that nicotinamide is a potent modulator of several proinflammatory cytokines. These findings demonstrate that nicotinamide has a potent immunomodulatory effect in vitro, and may have great potential for treatment of human inflammatory disease.**

PMID: 12519385 [PubMed - indexed for MEDLINE]

Trends Pharmacol Sci. 2003 May;24(5):228-32.

Nicotinamide: necessary nutrient emerges as a novel cytoprotectant for the brain.

Maiese K, Chong ZZ.

Division of Cellular and Molecular Cerebral Ischemia, Wayne State University, School of Medicine Detroit, St Antoine, MI 48201, USA. kmaiese@med.wayne.edu

Although usually identified as an essential cellular nutrient for cellular growth and maintenance, nicotinamide is under development as a novel cytoprotectant for acute and chronic neurodegenerative disorders. Here, we outline support for the premise that nicotinamide both prevents and reverses neuronal and vascular cell injury. **Nicotinamide fosters DNA integrity and maintains phosphatidylserine membrane asymmetry to prevent cellular inflammation, cellular phagocytosis and vascular thrombosis.** The downstream cellular and molecular cascades are considered vital for the cytoprotection offered by nicotinamide. These pathways encompass the modulation of Akt, the forkhead transcription factor FKHRL1, mitochondrial membrane potential, caspase activities and cellular energy metabolism, but remain independent of intracellular pH and mitogen-activated protein kinases. **As both a therapeutic agent and an investigational tool, nicotinamide offers new therapeutic strategies for degenerative disorders of the CNS.**

PMID: 12767721

Mol Cell Biochem. 1999 Mar;193(1-2):119-25.

Newly discovered anti-inflammatory properties of the benzamides and nicotinamides.

Pero RW, Axelsson B, Siemann D, Chaplin D, Dougherty G.

Department of Cell and Molecular Biology, University of Lund, Sweden.

Our laboratory has concentrated on the possible regulation the benzamides and nicotinamides may have on the processes of DNA repair and apoptosis. Recent reports have suggested that both apoptosis and inflammation are regulated by the transcription factor NF-kappaB. We have initiated studies regarding the hypothesis that the benzamides and nicotinamides could inhibit the production of tumor necrosis factor alpha (TNFalpha) and the inflammatory response as well as induce apoptosis via inhibition of NF-kappaB. Our data have shown that nicotinamide and two N-substituted benzamides, metoclopramide (MCA) and 3-chloroprocainamide (3-CPA), gave dose dependent inhibition of lipopolysacharide induced TNFalpha in the mouse within the dose range of 10-500 mg/kg. Moreover, lung edema was prevented in the rat by 3 x 50 mg/kg doses of 3-CPA or MCA, and 100-200 microM doses of MCA could also inhibit NF-kappaB in Hela cells. **Taken together these data strongly support the notion that benzamides and nicotinamides have potent anti-inflammatory and antitumor properties, because their primary mechanism of action is regulated by inhibition at the gene transcription level of NF-kappaB, which in turn inhibits TNFalpha and induces apoptosis.**

PMID: 10331648 [PubMed - indexed for MEDLINE]

Vitamin B1 (Thiamine) for Remyelination

Dr. Stern, at Columbia University, was using intraspinal injections of thiamine hydrochloride for MS back in the 1940s or so. Patients so treated did not appear to progress. Subsequent research indicates that thiamine helps promote remyelination (See below).

Multiple Sclerosis and other demyelinating diseases

To the Editor:

Multiple sclerosis has been defined as a chronic progressive disease of the central nervous system, or rather a series of syndromes based on several as-yet-undetermined causative factors. · The etiologic factor or factors are unknown, but Harrison · has emphasized its relationship to other demyelinating processes. The pathological change underlying multiple sclerosis is presumed to be demyelination in scattered areas of the brain and spinal cord in plaques of varying size. There is associated edema of the axons and, with progression, degeneration and loss of function. Vitamins B_1 and B_{12} axe both essential components of myelin. Because demyelination of long nerve axons in the spinal cord is characteristic of severe vitamin B deficiency and because this vitamin arrests demyelination in combined system disease, it has been used in the treatment of multiple sclerosis with varying results. · SUP>4~

On the theory that demyelination results from the lack of vitamin B1 and some factor or factors in liver extract, a therapeutic trial was initiated by the undersigned in 1943. The purpose of this letter is to report the results of that trial.

Materials and methods: Patients were selected on the basis of a history of neurologic deficits suggestive of multiple

sclerosis which had been confirmed by neurologic investigation and, in most patients, by a second opinion. The presence of paralysis was felt to be a contraindication to this type of therapy. Fourteen patients were followed up for periods varying from several months to 29 years (Table I).

Routine therapy consisted of intravenous thiamine hydrochloride, 150 mg., plus intramuscular injections of liver extract (Therapy was begun with Lederle's liver extract, but production ceased in the spring of 1972. Connaught Laboratory liver, extract was used for a period of nine months. Lilly's liver extract is now used.), 20 mcg (1 ml.), every seven to 10 days for a series of 10 treatments. The patient was then re-evaluated neurologically. Further treatment was recommended depending on the status of the neurologic deficit and the response.

Results and conclusions: The results in the treated patients are summarized in Table I. No patient had progression of the disease while on treatment. When symptoms recurred on cessation of treatment, they were controlled by resumption of therapy.

When vitamins B1 and B_{12} were given simultaneously to one patient (case 1) on two occasions (owing to sensitization to liver extract) the patient experienced progression of her deficit. When liver extract and vitamin B_1 therapy was resumed (following desensitization) she improved.

A trial of thiamine hydrochloride, 100 mg. daily by mouth, with regular liver extract therapy (case 4) led to return of symptoms. When routine therapy was again resumed all symptoms cleared. It would appear that some persons may not absorb vitamin B_1 through the gastrointestinal tract.

Patients treated in the early stages of the disease responded well and within a time span appropriate to the presumed underlying pathology of demyelination. Patients in whom the disease was more advanced responded more slowly. Early treatment of the disease or its recurrent symptoms seemed to be more important than the age of the patient. For example, one patient (case 1) now aged *55,* still returns for treatment when she considers it necessary because of a lowered sense of well-being, increased fatigue, and a tingling sensation in her hands and feet. Thirty-three years after the onset of her illness and after bed confinement for two years, she is active, does her housework, walks out alone without a cane and enjoys an active social life.

The exact stage of pathological change in any patient cannot be determined.[1] It is logical to assume, however, that the axis cylinders had not been destroyed in any of the patients in this study, even in case 3, a 59-year-old man who refused to accept active therapy until his disease, after many years, had induced almost total incapacity, including poor writing ability and spastic and ataxic gait with dragging of the left foot. His clinical improvement continues and we must assume that remyelination is taking place. At present, this man uses a cane only on the street, can step up with either foot and even uses a ladder. His manual dexterity is good and he writes well.

My experience, like that of Evers, · suggests that early treatment is important in producing symptomatic relief and a state of well being. In case 2, the patient was treated within six months of the onset of severe symptoms at age 43, made a rapid recovery and gave birth to a normal child two years later. On several occasions, because of irregular therapy, her symptoms recurred, but when treatment was resumed she improved rapidly. Now, at the age of 69, she is active and able to do her housework. In case 4, treatment was instituted within three years of the onset of the disease. The patient cooperated completely and therapy was continued without interruption. After nine months he stated that he felt perfectly well.

The effects of cessation and resumption of therapy are most clearly demonstrated in case 11. Following initial treatment from 1962 to 1964, her condition was improved and treatment was discontinued. In 1967, because of recurrence of symptoms, therapy was resumed on an irregular basis with subsequent improvement. In February 1971 the patient

returned with symptoms of fatigue, inability to work, loss of balance and staggering gait. She was not able to return for therapy until March 1972, at which time her neurologic condition had worsened. She had visual and auditory difficulty, scanning speech and poor writing ability, unsteady gait and poor sense of balance. Routine therapy was recommenced and by June 20 of the same year she was able to return to work as a typist and stated that she felt perfectly well.

The protracted and capricious natural history of multiple sclerosis precludes dogmatic statements regarding the effect of a new therapeutic modality. Furthermore, the exact diagnostic criteria of multiple sclerosis are uncertain, leading to a frequent diagnosis by exclusion appropriate to the uncertainty regarding etiology and pathogenesis. However, with regard to the therapy presented here, patients with two other types of demyelinating diseases have been successfully treated. One of these, a patient with advanced bulbar palsy, is now almost completely asymptomatic. The other, a patient with subacute combined sclerosis who was totally incapacitated, became neurologically entirely negative. My experience suggests that some factor or factors in liver extract, associated with vitamin B_1, can induce remyelination in patients suffering from multiple sclerosis and probably in other cases of demyelinating diseases. It is suggested that this clinical finding should now be subjected to detailed laboratory studies in order to enlarge its use or to circumscribe its limitations.

H.T. R. Mount, M.B., M.S.,F.R.C.S.[C], F.A.C.S.
203 - 340 McLeod St.,
Ottawa, Ont. K2P 1A4

References

1. WECHSLER IS: *Clinical neurology,* ninth ed. Philadelphia, WB Saunders, 1963
2. HAIws0N TR: *Principles of Internal Medicine,* sixth ed, vol 2. Toronto, McGraw-Hill, 1970, pp 1080-2016
3. LEHRER GM: Etiology, diagnosis and treatment of multiple sclerosis. *Mod Treat* 7: 1970
4. Cures for multiple sclerosis. *Br MedJ* I: *59,* 1970
5. NORMAN CS: Vitamin B,, plasma clearance in multiple sclerosis. *Jr I Med Sd 6:* 333, 1966
6. MERRITT, HN: *Textbook of Neurology,* fourth ed. Philadelphia, Lea and Febiger, 1967, pp 704-727
7. NAMEROW NS, THOMPSON LR:Plaques, symptoms, and the remitting course of multiple sclerosis. *Neurology (Minneap)* 19: 765, 1969
8. SIMPSON CA, NEWELL DJ, MILLER H: The treatment of multiple sclerosis with massive doses of hydroxycobalamin. *Neurology 15: 599, 1965*
9. EVERS J: Dietetic therapy of multiple sclerosis *Med Welt* 20: 1700, 1969

Extracted from **C.M.A. JOURNAL/JUNE 2, 1973/VOL. 108**

Taurine

J Neurosci Res. 2001 Nov 15;66(4):612-9.

Role of taurine in regulation of intracellular calcium level and neuroprotective function in cultured neurons.

Chen WQ, Jin H, Nguyen M, Carr J, Lee YJ, Hsu CC, Faiman MD, Schloss JV, Wu JY.

Department of Molecular Biosciences, University of Kansas, Lawrence, Kansas 66045, USA.

Glutamate-induced excitotoxicity has been implicated as an important mechanism underlying a variety of brain injuries and neurodegenerative diseases. Previously we have shown that taurine has protective effects against glutamate-induced neuronal injury in cultured neurons. Here we propose that the primary underlying mechanism of the neuroprotective function of taurine is due to its action in preventing or reducing glutamate-induced elevation of intracellular free calcium, [Ca(2+)](i). This hypothesis is supported by the following findings. First, taurine transport inhibitors, e.g., guanidinoethyl sulfonate and beta-alanine, have no effect on taurine's neuroprotective function, suggesting that taurine protects against glutamate-induced neuronal damage through its action on the extracellular membranes. Second, glutamate-induced elevation of [Ca(2+)](i) is reduced to the basal level upon addition of taurine. Third, pretreatment of cultured neurons with taurine prevents or greatly suppresses the elevation of [Ca(2+)](i) induced by glutamate. Furthermore, taurine was found to inhibit the influx but not the efflux of (45)Ca(2+) in cultured neurons. Taurine has little effect on the binding of [(3)H]glutamate to the agonist binding site and of [(3)H]MDL 105,519 to the glycine binding site of the N-methyl-D-aspartic acid receptors, suggesting that taurine inhibits (45)Ca(2+) influx through other mechanisms, including its inhibitory effect on the reverse mode of the Na(+)/Ca(2+) exchangers (Wu et al. [2000] In: Taurine 4: taurine and excitable tissues. New York: Kluwer Academic/Plenum Publishers. p 35-44) rather than serving as an antagonist to the N-methyl-D-aspartic acid receptors. Copyright 2001 Wiley-Liss, Inc.

PMID: 11746381

Dietary Exorphins · Morphine-Like compounds that fuel inflammation

MS and ALS patients would be well advised to eliminate all grains, cereals and bovine milk in order to stop exorphin production in their bodies!

Ann N Y Acad Sci. 2002 May;962:318-31.

Role of nitric oxide in inflammation-mediated neurodegeneration.

Liu B, Gao HM, Wang JY, Jeohn GH, Cooper CL, Hong JS.

Neuropharmacology Section, Laboratory of Pharmacology and Chemistry, National Institute of Environmental Health Sciences/National Institutes of Health, Research Triangle Park, North Carolina 27710, USA. liu3@niehs.nih.gov

Increasing evidence has suggested that inflammation in the brain is closely associated with the pathogenesis of several degenerative neurologic disorders, including Parkinson's disease, Alzheimer's diseases, multiple sclerosis, amyotrophic lateral sclerosis, and AIDS dementia. The hallmark of brain inflammation is the activation of glial

cells, especially that of microglia that produce a variety of proinflammatory and neurotoxic factors, including cytokines, fatty acid metabolites, free radicals--such as nitric oxide (NO) and superoxide. Excessive production of NO, as a consequence of nitric oxide synthase induction in activated glia, has been attributed to participate in neurodegeneration. Using primary mixed neuron-glia cultures and glia-enriched cultures prepared from embryonic rodent brain tissues, we have systemically studied the relationship between the production of NO and neurodegeneration in response to stimulation by the inflammagen lipopolysaccharide. This review summarizes our recent findings on the kinetics of NO generation, the relative contribution of microglia and astrocytes to NO accumulation, the relationship between NO production and neurodegeneration, and points of intervention along the pathways associated with NO generation to achieve neuroprotection. **We also describe our results relating to the effect of several opioid-related agents on microglial activation and neuroprotection. Among these agents, the opioid receptor antagonist naloxone, especially its non-opioid enantiomer (+)-naloxone, promises to be of potential therapeutic value for the treatment of inflammation-related diseases.**

PMID: 12076984

Alpha Lipoic Acid

Alpha Lipoic Acid as a Possible Treatment for Multiple Sclerosis

Scientists believe that oxidative injury may be associated with multiple sclerosis (MS). Mice with experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, were given Alpha Lipoic Acid to treat. The mice showed a reduction of encephalomyelitis symptoms of between 23% - 100%, with minimal inflammation, demyelination and axonal loss in the spinal cords. The scientists conducting the research concluded, "ALA is highly effective at suppressing and treating EAE and does so by inhibiting T cell trafficking into the spinal cord, perhaps by acting as a matrix metalloproteinase inhibitor." While emphasizing that more research is required, researchers believe that ALA may have potential as a treatment for MS.

Also, high iron levels in the gray matter (brain) of MS patients has been linked to both cognitive and physical deficits (See below)! Interestingly, alpha lipoic acid appears to help decrease iron in tissues (The pharmaceutical desferrioxamine also does this quite effectively). Abstracts follow the *Science Daily* article below.

http://www.sciencedaily.com/releases/2003/10/031022062049.htm

Source: University At Buffalo

Date: 2003-10-22

Gray Matter Damage In The Brain Of MS Patients Linked To Cognitive, Physical Deficits

BUFFALO, N.Y. -- The mental impairment and problems with walking experienced by patients with multiple sclerosis (MS) are linked to damage in the brain's gray matter, with MRI findings suggesting the damage is due to toxic deposits of iron, researchers from the University at Buffalo have shown for the first time. Previous breakthrough work by the team had linked deep gray matter iron deposits to the disease course of MS, brain atrophy and overall disability, but not to cognition or ambulation. Results of these latest studies were presented today (Oct. 21, 2003) at the annual meeting of the American Neurological Association in San Francisco.

The researchers, affiliated with the Buffalo Neuroimaging Analysis Center (BNAC) and Jacobs Neurological Institute, use specialized, computer-assisted magnetic resonance imaging (MRI) technology to focus on hypointensity, or unnatural darkness, of gray matter structures as seen on so-called T2-weighted images. This condition is referred to as T2 hypointensity. Using this approach, they were able to show that structures in the brain's deep gray matter of MS patients contained T2 hypointensity compared with normal individuals, suggesting higher-than-normal levels of iron deposits, and confirmed the relationship of T2 hypointensity to MS symptoms.

"Traditionally, we thought MS was strictly a 'white matter disease,' involving the brain's neural pathways that allow various gray-matter structures to communicate with each other," said Rohit Bakshi, M.D., UB associate professor of neurology, first author on the new studies and founding director of the BNAC. "Through our computerized imaging analysis capabilities, we were able to visualize gray matter structures deep in the brain of MS patients and found some to be atrophied.

"We also found MRI evidence of abnormally high levels of iron," he said. "Moreover, these changes weren't associated with the amount of white-matter damage, so this was all new information. If we're going to treat this disease, we have to know where the damage is."

The finding concerning gray matter atrophy resulted from the researchers' work with a brain structure called the caudate nucleus, which is an important nerve center for controlling movement and cognitive processing. Other laboratories have studied the role of the caudate nucleus in Alzheimer's disease and Huntington's disease, but the BNAC is the only center studying it in MS patients using state-of-the-art MRI techniques. The current studies take the BNAC's previous research to the next level, in an effort to determine the role of excess iron in specific MS disabilities. Bakshi and colleagues tested walking ability and cognitive impairment respectively in two groups of MS patients that underwent the specialized MRI brain scans to assess T2 hypointensity of the gray matter structures thought to be involved in these conditions.

The ambulatory study involved 41 MS patients who completed a timed 25-foot walk, a standard measure of physical dysfunction. These times were compared with T2 hypointensity in the gray matter, as well as brain atrophy and additional anatomical brain changes known to occur in MS. Results showed that T2 hypointensity was the only brain change directly associated with impaired walking ability, and the strongest association with walking ability pointed to the brain structure known as the dentate nucleus. This structure exists deep in the cerebellum, the brain region responsible for coordination and smooth movement of the limbs.

The study of cognitive impairment involved 28 MS patients who took tests measuring learning, speed of information processing and working memory. Test results were compiled into an attention/memory composite, which was compared with the same measures of brain change used in the ambulation assessment. T2 hypointensity in the brain's deep gray matter structures was the only measure that predicted cognitive impairment in these patients, results showed.

"We suspect that MS patients have defective blood-brain barriers, the cell layer that prevents potentially toxic substances from entering the brain," Bakshi said. "Excessive iron entering the brain may damage the deep gray matter structures through generation of free radicals and lipid peroxidation, as well as inflammation, all of which would destroy neurons. We have tissue samples from two autopsied brains showing high iron levels in these gray matter structures in patients with MS compared to controls."

Bakshi said the other possibility is that high levels of iron are a result of the neurodegenerative process that occurs in MS. "When brain cells are destroyed, in aging for example, iron levels increase in the brain. High levels of iron also are seen in Alzheimer's and Parkinson-related diseases. There is still a debate about cause-effect of iron in all of these conditions.

"We do think, however, that hypointensity in the deep gray matter is a strong predictor of disability, progression of the disease and subsequent brain atrophy in MS," he said. "If future longitudinal studies support these findings, it may be possible to design a new treatment to prevent iron build-up, which could prove beneficial to MS patients. However, we must have further studies to draw definitive conclusions," stated Bakshi.

Additional researchers on the studies were Christopher Tjoa, a first-year UB medical student; Ralph Benedict, Ph.D., UB neuropsychologist and associate professor of neurology; Andrew Fabiano, third-year UB medical student; Jitendra Sharma, M.D., a graduate student at Roswell Park Cancer Institute; Robert Bermel, fourth-year UB medical student; Frederick E. Munschauer, M.D., professor and chair of the UB Department of Neurology, and Bianca Weinstock-Guttman, M.D., assistant professor of neurology.

The studies were funded by grants from the National Institutes of Health, National Science Foundation and the National Multiple Sclerosis Society, and by an Alpha Omega Alpha medical school research fellowship and an American Academy of Neurology Student Interest in Neurology Summer Scholarship.

This story has been adapted from a news release issued by University At Buffalo.

Exp Eye Res. 2003 Feb;76(2):241-8.

Alpha lipoic acid changes iron uptake and storage in lens epithelial cells.

Goralska M, Dackor R, Holley B, McGahan MC.

Department of Molecular Biomedical Sciences, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, USA.

Alpha lipoic acid (LA) is a cofactor in mitochondrial dehydrogenase complexes. Previous studies have shown that when administered exogenously LA has antioxidant properties, which include free radical scavenging, metal chelation and regeneration of other antioxidants. The cells convert LA into dihydroplipoic acid (DHLA), which in the presence of iron can act as a prooxidant. In vitro DHLA reduces Fe(+3) to Fe(+2) and removes iron from ferritin, increasing the risk of Fe catalyzed free radical formation. In the present study we examined the in vivo effects of lipoic acid treatment on Fe metabolism in cultured lens epithelial cells, and found that LA decreases Fe uptake from transferrin, increases Fe deposition into ferritin and increases the concentration of this protein. When administered together with ascorbic acid, lipoic acid changes the characteristic heavy to light chain ratio of ferritin makeup. The decreased Fe uptake and increased storage diminishes the size of the cytosolic highly reactive Fe pool (LIP). These changes are associated with increased cell resistance to H(2)O(2) challenge. Therefore, LA may reduce the risk of Fe induced oxidative damage and also might be useful as a treatment of Fe overload. Copyright 2003 Elsevier Science Ltd.

PMID: 12565812 [PubMed - indexed for MEDLINE]

Redox Rep. 2001;6(5):327-34.

Alpha-lipoic acid and alpha-lipoamide prevent oxidant-induced lysosomal rupture and apoptosis.

Persson HL, Svensson AI, Brunk UT.

Division of Pathology II, Faculty of Health Sciences, Linkoping University, Sweden. lennart.persson@lio.se

Alpha-lipoic acid (LA) and its corresponding derivative, alpha-lipoamide (LM), have been described as antioxidants, but the mechanisms of their putative antioxidant effects remain largely uncharacterised. The vicinal thiols present in the reduced forms of these compounds suggest that they might possess metal chelating properties. We have shown previously that cell death caused by oxidants may be initiated by lysosomal rupture and that this latter event may involve intralysosomal iron which catalyzes Fenton-type chemistry and resultant peroxidative damage to lysosomal membranes. Here, using cultured J774 cells as a model, we show that both LA and LM stabilize lysosomes against oxidative stress, probably by chelating intralysosomal iron and, consequently, preventing intralysosomal Fenton reactions. In preventing oxidant-mediated apoptosis, LM is significantly more effective than LA, as would be expected from their differing capacities to enter cells and concentrate within the acidic lysosomal compartment. As previously reported, the powerful

iron-chelator, desferrioxamine (Des) (which also locates within the lysosomal compartment), also provides protection against oxidant-mediated cell death. Interestingly, although Des enhances the partial protection afforded by LA, it confers no additional protection when added with LM. Therefore, the antioxidant actions of LA and LM may arise from intralysosomal iron chelation, with LM being more effective in this regard.

PMID: 11778851 [PubMed - indexed for MEDLINE]

Acetyl-L-Carnitine

Neurochem Res. 2003 Sep;28(9):1321-8.

Disruption of thiol homeostasis and nitrosative stress in the cerebrospinal fluid of patients with active multiple sclerosis: evidence for a protective role of acetylcarnitine.

Calabrese V, Scapagnini G, Ravagna A, Bella R, Butterfield DA, Calvani M, Pennisi G, Giuffrida Stella AM.

Department of Chemistry, Section of Biochemistry and Molecular Biology. Faculty of Medicine, University of Catania, Catania, Italy. calabres@mbox.unict.it

Recent studies suggest that NO and its reactive derivative peroxynitrite are implicated in the pathogenesis of multiple sclerosis (MS). Patients dying with MS demonstrate increased astrocytic inducible nitric oxide synthase activity, as well as increased levels of iNOS mRNA. Peroxynitrite is a strong oxidant capable of damaging target tissues, particularly the brain, which is known to be endowed with poor antioxidant buffering capacity. Inducible nitric oxide synthase is upregulated in the central nervous system (CNS) of animals with experimental allergic encephalomyelitis (EAE) and in patients with MS. We have recently demonstrated in patients with active MS a significant increase of NOS activity associated with increased nitration of proteins in the cerebrospinal fluid (CSF). Acetylcarnitine is proposed as a therapeutic agent for several neurodegenerative disorders. Accordingly, in the present study, MS patients were treated for 6 months with acetylcarnitine and compared with untreated MS subjects or with patients noninflammatory neurological conditions, taken as controls. Western blot analysis showed in MS patients increased nitrosative stress associated with a significant decrease of reduced glutathione (GSH). Increased levels of oxidized glutathione (GSSG) and nitrosothiols were also observed. Interestingly, treatment of MS patients with acetylcarnitine resulted in decreased CSF levels of NO reactive metabolites and protein nitration, as well as increased content of GSH and GSH/GSSG ratio. Our data sustain the hypothesis that nitrosative stress is a major consequence of NO produced in MS-affected CNS and

implicate a possible important role for acetylcarnitine in protecting brain against nitrosative stress, which may underlie the pathogenesis of MS.

PMID: 12938853

Curr Med Chem. 2003 Dec;10(23):2599-610.

Intracellular thiol concentration modulating inflammatory response: influence on the regulation of cell functions through cysteine prodrug approach.

Santangelo F.

Pharma R&D, Zambon Group Spa, Via Lillo del Duca, 10, 20091 Bresso, Milano, Italy. francesco.santangelo@fastwebnet.it

Oxidative stress is defined as the consequence of overpowering of the immune system's reaction, which causes increased production of the reactive oxidative species (ROS) greater than the antioxidant protection. Tissue injury and oxidation of the circulating molecules may be the consequences. Moreover, the sulphur-containing amino acids (SAA) fate is perturbed during stress. The altered biochemical rules during inflammation weaken the anti-oxidant mechanism, and the extra-supply of SAA under inflammatory conditions can help to restore homeostasis. In brief, the main biochemical steps during inflammation are: The production of Cytokines, Acute Phase Protein, and Glutathione (GSH) pool are strongly modified during inflammation. * The GSH participates in many important physiological processes controlling the homeostasis of the cells. * A higher demand of Cysteine (Cys) supply causes difficulties in maintaining a constant GSH level. * The role of GSH as a key regulator of thiol redox intracellular balance is established. This reveals that GSH is essential in regulating the cell's life cycle and that the reduction of intracellular GSH contributes to chronic inflammation. The fact that Cys availability is generally a limiting factor for the GSH synthesis stimulated the development of a pharmacologically useful Cys pro-drug. The simplest derivative is N-acetylcysteine (NAC), which appears to be the prototype of all Cys suppliers. Different approaches are presented here.

PMID: 14529474

Neurosci Lett. 2002 Sep 6;329(3):334-8.

Acetyl-L-carnitine shows neuroprotective and neurotrophic activity in primary culture of rat

embryo motoneurons.

Bigini P, Larini S, Pasquali C, Muzio V, Mennini T.

Laboratory for Receptor Pharmacology, Mario Negri Institute for Pharmacological Research, Via Eritrea, 62, 20157 Milan, Italy. bigini@marionegri.it

We evaluated the role of acetyl-L-carnitine (ALCAR) in protecting primary motoneuron cultures exposed to excitotoxic agents or serum-brain derived neurotrophic factor (BDNF) deprived. To exclude that ALCAR works as a metabolic source, we compared its effects with those of L-carnitine (L-CAR), that seems to have no neurotrophic effect. A concentration of 10 mM ALCAR, but not L-CAR, significantly reduced the toxic effect of 50 microM N-methyl-D-aspartate (NMDA, % viability: NMDA 45.4+/-2.80, NMDA+ALCAR 90.8+/-11.8; P<0.01) and of 5 microM kainate in cultured motoneurons (% viability: kainate 40.66+/-10.73; kainate+ALCAR 63.80+/-13.88; P<0.05). The effect was due to a shift to the right of the dose-response curve for kainate (EC50 for kainate 5.99+/-1.012 microM; kainate+ALCAR 8.62+/-1.13 microM; P<0.05). ALCAR, but not L-CAR, significantly protected against BDNF and serum-deprivation reducing the apoptotic cell death (% viability respect to control: without BDNF/serum 61.8+/-13.3: without BDNF/serum+ALCAR 111.8+/-13.9; P<0.01). Immunocytochemistry showed an increase in choline acethyltransferase and tyrosine kinaseB receptors in motoneurons treated with ALCAR but not with L-CAR. These results suggest that ALCAR treatment improves the motoneurons activity, acting as a neurotrophic factor.

PMID: 12183043 [PubMed - indexed for MEDLINE]

Proc Natl Acad Sci U S A. 2002 Mar 5;99(5):3258-63. Epub 2002 Feb 26.

Thyroid hormone activates oligodendrocyte precursors and increases a myelin-forming protein and NGF content in the spinal cord during experimental allergic encephalomyelitis.

Calza L, **Fernandez M**, **Giuliani A**, **Aloe L**, **Giardino L**.

Department of Veterinary Morphophysiology and Animal Production, University of Bologna, 40064 Ozzano Emilia, Bologna, Italy. lcalza@vet.unibo.it

Remyelination in the adult central nervous system has been demonstrated in different experimental models of demyelinating diseases. However, there is no clear evidence that remyelination occurs in multiple sclerosis, the most diffuse demyelinating disease. In this article, we explore the possibility of promoting myelination in experimental allergic encephalomyelitis, a widely used experimental model of multiple sclerosis, by recruiting progenitors and channeling them into oligodendroglial lineage through administration of thyroid hormone (T4). A large number of proliferating cells (BrdUrd uptake and Ki67-IR) and the _expression of markers for undifferentiated precursors (nestin) increased in the

subventricular zone and spinal cord of experimental allergic encephalomyelitis animals. T4 administration reduces proliferation and nestin-immunoreactivity and up-regulates _expression of markers for oligodendrocyte progenitors [polysialylated-neural cell adhesion molecule (PSA-NCAM), O4, A2B5] and mature oligodendrocytes (myelin basic protein) in the spinal cord, olfactory bulb, and subventricular zone.

PMID: 11867745 [PubMed - indexed for MEDLINE]

Complete Paper: http://www.pubmedcentral.gov/picrender.fcgi?artid=122506&blobtype=pdf

Neurology. 2003 Oct 28;61(8):1113-20. Related Articles, Links

Glutamate uptake by oligodendrocytes: Implications for excitotoxicity in multiple sclerosis.

Pitt D, **Nagelmeier IE**, **Wilson HC**, **Raine CS**.

Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA. dfpitt@yahoo.com

BACKGROUND: Excitotoxic damage is a common pathologic event in a number of neurologic diseases occurring after accumulation of excess extracellular glutamate in the CNS and subsequent overstimulation of glutamate receptors. In gray matter, astrocytes take up synaptically released glutamate and are thus key cells in maintaining glutamate homeostasis. In white matter, oligodendrocytes have been shown to express glutamate transporters, but their role in extracellular glutamate removal is unclear. OBJECTIVE: To investigate whether cultured human fetal oligodendrocytes functionally express the main glutamate transporters EAAT-1 and EAAT-2. METHODS: Cultures of fetal human oligodendrocytes were examined by immunocytochemistry and [3H]glutamate uptake, and the findings were correlated with glutamate transporter _expression in normal and multiple sclerosis (MS) CNS tissue. RESULTS: Both EAAT-1 and EAAT-2 were expressed by human oligodendrocytes in vitro. Incubation of oligodendrocytes with the proinflammatory cytokine tumor necrosis factor-alpha (TNFalpha) reduced EAAT-1 _expression and inhibited glutamate uptake by >75%. Furthermore, in normal human white matter, oligodendrocytes were found to be the predominant cells to express EAAT-1 and EAAT-2, both at the mRNA and at the protein level. A small number of astrocytes in white matter expressed these receptors, more so EAAT-1 than EAAT-2. In MS white matter, oligodendrocytes lost _expression of EAAT-1 and EAAT-2 receptors in the lesion vicinity. CONCLUSIONS: Oligodendrocytes appear to be predominant cells for glutamate clearance in human white matter. Glutamate receptor _expression and glutamate removal were defective in MS white matter, possibly mediated by TNFalpha, changes that might underlie high extracellular glutamate and an increased risk for glutamate excitotoxicity.

PMID: 14581674 [PubMed - indexed for MEDLINE]

Phytother Res. 2000 Sep;14(6):466-8. Related Articles, Links

Extract prepared from the bark of Cinnamomum cassia Blume prevents glutamate-induced neuronal death in cultured cerebellar granule cells.

Shimada Y, **Goto H**, **Kogure T**, **Kohta K**, **Shintani T**, **Itoh T**, **Terasawa K**.

Department of Japanese Oriental Medicine, Faculty of Medicine, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan. shimada@ms.toyama-mpu.ac.jp

We studied the protective effect of a water extract from the bark of Cinnamomum cassia Blume on glutamate-induced neuronal death by MTT assay and its action on (45)Ca(2+) influx using cultured rat cerebellar granule cells. In a dose-dependent manner, this extract (10(-5)-10(-4) g/mL) significantly protected against glutamate-induced cell death and also inhibited glutamate-induced (45)Ca(2+) influx. These results suggest that the bark of Cinnamomum cassia has a protective effect on glutamate-induced neuronal death through the inhibition of Ca(2+) influx. Copyright 2000 John Wiley & Sons, Ltd.

PMID: 10960905 [PubMed - indexed for MEDLINE]

Pregnenolone

http://en.wikipedia.org/wiki/Pregnenolone

http://www.networkforhealth.com/images/steroidpathways.jpg - Prenenolone --> progesterone

Steroids. 2000 Oct-Nov;65(10-11):605-12. Links

Comment in:

Hum Reprod. 2001 Aug;16(8):1542.

Progesterone as a neuroactive neurosteroid, with special reference to the effect of progesterone on myelination.

Baulieu E, **Schumacher M**.

INSERM U 488, 80 rue du Général Leclerc, 94276, Le Kremlin-Bic etre, France. baulieu@kb.inserm.fr

Some steroids are synthesized within the central and peripheral nervous system, mostly by glial cells. These are known as neurosteroids. In the brain, certain neurosteroids have been shown to act directly on membrane receptors for neurotransmitters. For example, progesterone inhibits the neuronal nicotinic acetylcholine receptor, whereas its 3alpha,5alpha-reduced metabolite 3alpha, 5alpha-tetrahydroprogesterone (allopregnanolone) activates the type A gamma-aminobutyric acid receptor complex. Besides these effects, neurosteroids also regulate important glial functions, such as the synthesis of myelin proteins. Thus, in cultures of glial cells prepared from neonatal rat brain, progesterone increases the number of oligodendrocytes expressing the myelin basic protein (MBP) and the 2',3'-cyclic

nucleotide-3'-phosphodiesterase (CNPase). An important role for neurosteroids in myelin repair has been demonstrated in the rodent sciatic nerve, where progesterone and its direct precursor pregnenolone are synthesized by Schwann cells. After cryolesion of the male mouse sciatic nerve, blocking the local synthesis or action of progesterone impairs remyelination of the regenerating axons, whereas administration of progesterone to the lesion site promotes the formation of new myelin sheaths.

PMID: 11108866 [PubMed - indexed for MEDLINE]

Trends Endocrinol Metab. 2008 Oct;19(8):300-7. Epub 2008 Sep 2. Links

Neurosteroids as modulators of neurogenesis and neuronal survival.

Charalampopoulos I, **Remboutsika E**, **Margioris AN**, **Gravanis A**.

Department of Pharmacology, School of Medicine, University of Crete, Heraklion 71003, Greece.

Neurons and glia in the central nervous system express the necessary enzymes for the synthesis of neurosteroids that are produced in concentrations high enough to exert paracrine effects. Synthesis of brain neurosteroids declines with age, during stressful conditions (including major depression, chronic psychological stress), and in chronic inflammatory and neurodegenerative diseases. Recent reports associate the decrease of brain neurosteroids to neuronal dysfunction and degeneration. This review summarizes the recent findings on how the most studied neurosteroids (dehydroepiandrosterone, pregnenolone and their sulphate esters, progesterone and allopregnanolone) affect neuronal survival, neurite outgrowth and neurogenesis; furthermore, this review discusses potential applications of these neurosteroids in the therapeutic management of neurodegenerative conditions, including that of age-related brain atrophy.

PMID: 18771935

comparative or controversial nature, or usefulness of any information contained or referenced in this document. Dr. Anthony G. Payne, Nepsis Institute (Mexico) and Weller Health Institute do not assume any risk whatsoever for your use of this document or any associated websites or for the information contained therein. Health-related information and opinions change frequently and therefore information contained in this document may be outdated, incomplete or incorrect. All statements made about products in this document or any associated websites have not been evaluated by the Food and Drug Administration (FDA). Use of this document and any associated web sites does not create an expressed or implied professional or other relationship.
