Therapeutic value of citicoline in the treatment of glaucoma (computerized and automated perimetric investigation).

Clinica Oculistica I, Universita Di Roma La Sapienza, Italia.

The favourable neurotrophic effects obtained by means of the intramuscular administration of citicoline, one of the intermediate compounds of phospholipids, on the visual field of patients suffering from open-angle glaucoma are referred. The drug was administered at the dose of 1 gm for ten consecutive days. Visual field was examined by means of central computerized perimetry and automated perimetry. All patients had well controlled intraocular pressure through beta-blockers, but presented characteristic glaucomatous perimetric defects. It is suggested that citicoline might be administered as a useful complement to conventional hypotensive therapy, since it acts positively on the glaucomatous optic nerve damage.

Cytidine-5'-diphosphocholine (citicoline) improves retinal and cortical responses in patients with glaucoma.

Parisi V, Manni G, Colacino G, Bucci MG.
Cattedra di Clinica Oculistica, Universita' di Roma Tor Vergata, Rome, Italy. vparisi@tin.it

PURPOSE: To evaluate the effects of cytidine-5'-diphosphocholine (citicoline) on retinal function and on cortical responses in patients with glaucoma.

DESIGN: Randomized clinical trial.

PARTICIPANTS: Forty patients with open-angle glaucoma were randomly divided into two age-matched groups: citicoline group ([GC] n = 25) and placebo group ([GP] n = 15).

METHODS: The GC patients were treated with Neuroton (citicoline, 1000 mg/day intramuscularly) for 60 days; GP patients were treated with placebo (physiologic solution with additives) for 60 days. After 120 days of washout (day 180), the GC patients were divided into two age-matched groups: in 10 patients (GC1 group) the washout was prolonged for a further 120 days; in 15 patients (GC2 group) a second 60-day period of citicoline treatment was followed by a second 120-day period of washout. At day 180, the washout was extended for another 180 days in GP patients. In all subjects, retinal and cortical responses were evaluated by simultaneous recordings of visual evoked potentials (VEPs) and pattern-electroretinograms (PERGs) at baseline, after 60 days, and after 180 days. At day 300, VEPs and PERGs were also evaluated in GC1 patients, and at 240 and 360 days in GC2 and GP patients.

MAIN OUTCOME MEASURES: Visual evoked potential parameters (P100 latency and N75-P100 amplitude); PERG parameters (P50 latency and P50-N95 amplitude); and intraocular pressure.

RESULTS: The GP patients displayed similar VEP and PERG parameters in all examinations performed. In GC patients, the treatment with citicoline induced a significant (P < 0.01) improvement of VEP and PERG parameters, and their values were significantly different (P < 0.01) with respect to those of GP patients (P < 0.01). Visual evoked potentials and PERGs, recorded in GC patients after washout, revealed that although there was a worsening trend, the electrophysiologic improvement was still maintained. After a second period of washout, GC1 patients had VEP and PERG parameters similar (P > 0.05) to baseline ones and to those of GP patients. In GC2 patients, a second period of citicoline treatment induced a further (P < 0.01) improvement of VEP and PERG parameters.

CONCLUSION: Citicoline may induce an improvement of the retinal and of the visual pathway function in patients with glaucoma.

Citicoline has a protective effect on damaged retinal ganglion cells in mouse culture retina.

Oshitari T, Fujimoto N, Adachi-Usami E.
Department of Ophthalmology and Visual Science, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. tani@aol.com

Some clinical reports indicate that exogenous CDP-choline (citicoline) may have a therapeutic effect in patients with glaucoma. However, the precise effect of citicoline on damaged retinal ganglion cells (RGCs) remains to be explained. We performed tissue culture of mouse retinal explants and investigated the effect of citicoline on damaged RGCs by the quantitative analysis of TdT-DUTP terminal nick-end labeling (TUNEL) staining and the assessment of the number of regenerating neurites. The TUNEL-positive ratio in 0.1-10 micromol/l citicoline-treated retina was very low, and the number of regenerating neurites increased more than in control retina. Our findings suggest that citicoline has a protective effect on damaged RGCs in tissue culture of retina.
Brain-derived neurotrophic factor enhances neurite regeneration from retinal ganglion cells in aged human retina in vitro.


To investigate the capability of neurite regeneration from retinal ganglion cells (RGCs) in an adult human retina and to evaluate the effect of neurotrophin on the neurite regeneration, an in vitro model for retinal explants was developed. A human retina was obtained from a 70 year old patient with retrobulbar carcinoma. The retina was excised and the retinal explants were cultured in serum-free medium with or without brain-derived neurotrophic factor. The capability of neurite regeneration was evaluated by counting the numbers of outgrowing neurites outside the retinal explants. In culture without brain-derived neurotrophic factor (control), there was no neurite outgrowth from the retinal explants after 2 days. And at 3 days in culture, a small number of outgrowing neurites were first observed outside the retinal explants. In contrast, within 24 hr in culture with brain-derived neurotrophic factor, there were a considerable number of elongating neurites with spread growth cones from the retinal explants. Immunohistochemical analysis revealed that these neurites were derived from RGCs. The addition of brain-derived neurotrophic factor increased the number of outgrowing neurites approximately 10-fold compared to that of the control at 3 days in culture. The enhancement of neurite regeneration induced by brain-derived neurotrophic factor continued for longer than 1 week in culture. In conclusion, an aged human retina can regenerate neurites from RGCs in vitro and brain-derived neurotrophic factor significantly promotes the regeneration.

The effect of caspase inhibitors and neurotrophic factors on damaged retinal ganglion cells.

Oshitari T, Adachi-Usami E.

Department of Ophthalmology and Visual Science, Graduate School of Medicine, Chiba University, Japan. tarii@aol.com

To elucidate the role of caspase inhibitors and neurotrophic factors in retinal ganglion cell (RGC) death and regeneration, we cultured mouse retinal explants in the presence of caspase-1, -3, -8, or -9 inhibitors, brain-derived neurotrophic factor (BDNF) and ciliary neurotrophic factor (CNTF) in serum-free culture media. We quantified apoptosis by TUNEL staining in RGCs and assessed the number of regenerating neurites. Apoptosis of RGCs treated with all caspase inhibitors or with neurotrophic factors was significantly reduced and the number of regenerating neurites was significantly greater than controls (p < 0.05). Our findings indicate that caspase-1, -3, -8, -9 play a critical role in explanted RGC death and may be ideal targets of neuroprotection and regeneration of damaged RGCs.

Oral citicoline treatment improves visual pathway function in glaucoma.

Rejdak R, Toczołowski J, Kurkowski J, Kamiński ML, Rejdak K, Stelmasiak Z, Grieb P.

2nd Department of Ophthalmology, Medical University, Lublin, Poland.

BACKGROUND: Increased latency and reduced amplitude of visual evoked potentials (VEP), frequently encountered in ocular hypertension or open-angle glaucoma, suggest slowed neural conduction in the visual pathways. An improvement in VEP latency and amplitude has been reported following repeated intramuscular injections of citicoline, a neuroprotective drug. Our aim was to find whether citicoline given orally would produce a similar effect.

MATERIAL/METHODS: VEP latency and amplitude were measured in 21 glaucomatous eyes prior to and after two bi-weekly courses of citicoline taken orally in a dose of 1 gram/day. The treatment courses were separated by a two-week break; post-treatment VEP measurement was performed two weeks after the end of the second treatment.

RESULTS: 62% of the eyes showed a response to the treatment, with VEP latency reduced from 123.5 (3.9 SEM) ms to 111.9 (1.9 SEM) ms (P=0.0008), and VEP amplitude increased from 6.56 (1.39 SEM) to 7.88 (1.16 SEM) (P=0.04).

CONCLUSIONS: Citicoline given orally improves visual evoked potentials in some glaucoma patients.
Cytidine 5'-diphosphocholine, CDP-choline, or citicoline is an essential intermediate in the biosynthetic pathway of structural phospholipids in cell membranes, particularly phosphatidylcholine. Following administration by both the oral and parenteral routes, citicoline releases its two main components, cytidine and choline. Absorption by the oral route is virtually complete, and bioavailability by the oral route is therefore approximately the same as by the intravenous route. Once absorbed, citicoline is widely distributed throughout the body, crosses the blood-brain barrier and reaches the central nervous system (CNS), where it is incorporated into the membrane and microsomal phospholipid fraction. Citicoline activates biosynthesis of structural phospholipids of neuronal membranes, increases brain metabolism, and acts upon the levels of different neurotransmitters. Thus, citicoline has been experimentally shown to increase norepinephrine and dopamine levels in the CNS. Owing to these pharmacological mechanisms, citicoline has a neuroprotective effect in hypoxic and ischemic conditions, decreasing the volume of ischemic lesion, and also improves learning and memory performance in animal models of brain aging. In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na+/K+ATPase, to inhibit activation of certain phospholipases, and to accelerate reabsorption of cerebral edema in various experimental models. Citicoline has also been shown to be able to inhibit mechanisms of apoptosis associated to cerebral ischemia and in certain neurodegeneration models, and to potentiate neuroplasticity mechanisms. Citicoline is a safe drug, as shown by the toxicological tests conducted, that has no significant systemic cholinergic effects and is a well tolerated product. These pharmacological characteristics and the action mechanisms of citicoline suggest that this product may be indicated for treatment of cerebral vascular disease, head trauma (HT) of varying severity, and cognitive disorders of different causes. In studies conducted in the treatment of patients with HT, citicoline was able to accelerate recovery from post-traumatic coma and neurological deficits, achieving an improved final functional outcome, and to shorten hospital stay in these patients. Citicoline also improved the mnesic and cognitive disorders seen after HT of minor severity that constitute the so-called post-concussional syndrome. In the treatment of patients with acute ischemic cerebral vascular disease, citicoline accelerates recovery of consciousness and motor deficit, achieves a better final outcome, and facilitates rehabilitation of these patients. The other major indication of citicoline is for treatment of senile cognitive impairment, either secondary to degenerative diseases (e.g. Alzheimer disease) or to chronic cerebral vascular disease. In patients with chronic cerebral ischemia, citicoline improves scores in cognitive rating scales, while in patients with senile dementia of the Alzheimer type it stops the course of disease, and neuroendocrine, neuroimmunomodulatory, and neurophysiological benefits have been reported. Citicoline has also been shown to be effective in Parkinson disease, drug addictions, and alcoholism, as well as in amblyopia and glaucoma. No serious side effects have occurred in any series of patients treated with citicoline, which attests to the safety of treatment with citicoline. (c) 2006 Prous Science. All rights reserved.
Cytidine-5’-diphosphocholine (Citocline): a pilot study in patients with non-arteritic ischaemic optic neuropathy.

Parisi V, Coppola G, Ziccardi L, Gallinaro G, Falsini B.
Department of Neurophysiology of Vision and Neurphthalmology, G.B. Bietti Eye Foundation-IRCCS, Rome, Italy. vparisi@tin.it

BACKGROUND AND PURPOSE: Our work evaluates visual function before and after treatment with cytidine-5-diphosphocholine (Citocline) in patients with non-arteritic ischaemic optic neuropathy (NION). METHODS: Twenty-six patients in which at least 6 months elapsed from NION, were randomly divided into two age-similar groups: 14 patients had Citocline (Cebrolux-Tubilux, Italy, 1600 mg/diem for 60 days, followed by a 120-day period of wash out, days 60-180) (T-NION); 12 patients had no treatment during the same period (NT-NION). At day 180, in T-NION a second period of treatment (days 181-240) followed by a wash-out (days 241-360) was performed. Fourteen age-matched healthy subjects provided normative data. In all patients, pattern-electroretinogram (PERG), visual evoked potentials (VEPs) and visual acuity (VA) measurements were performed at baseline and at days 60 and 180. In T-NION, further measurements were achieved at days 240 and 360. RESULTS: At baseline, NT-NION and T-NION patients showed abnormal PERGs and VEPs, and reduced VA, compared to controls. At the end of treatment (days 60 and 240), T-NION patients showed improvement (P < 0.01) of PERGs, VEPs parameters and VA, compared to pre-treatment values. After wash out, functional improvements persisted compared to baseline. No changes in NT-NION patients were observed. CONCLUSIONS: Our results suggest a beneficial effect of oral Citocline in NION.

CDP-choline protects motor neurons against apoptotic changes in a model of chronic glutamate excitotoxicity in vitro.

Matyja E, Taraszewska A, Nagańska E, Grieb P, Rafałowska J.
Department of Experimental and Clinical Neurology, Medical Research Centre, Polish Academy of Science, 5 Pawinskiego Str., 02-106 Warsaw, Poland, tel: +48 22 608 65 43, fax: +48 22 668 55 32, Email: matyja@cmdik.pan.pl.

Cytidine-5-diphosphocholine (CDP-choline, citicoline) is an endogenous nucleoside involved in generation of phospholipids, membrane formation and its repair. It demonstrates beneficial effects in certain central nervous system injury models, including cerebral ischaemia, neurodegenerative disorders and spinal cord injury. Defective neuronal and/or glial glutamate transport is claimed to contribute to progressive loss of motor neurons (MNs) in amyotrophic lateral sclerosis (ALS). Our previous ultrastructural studies, performed on an organotypic tissue culture model of chronic glutamate excitotoxicity, documented a subset of various modes of MN death including necrotic, apoptotic and autophagocytic cell injury. The aim of this ultrastructural study was to determine the potential neuroprotective effect of CDP-choline on neuronal changes in a glutamate excitotoxic ALS model in vitro. Organotypic cultures of the rat lumbar spinal cord subjected to 100 microM DL-threo-b-hydroxyaspartate (THA) were pretreated with 100 microM of CDP-choline. The exposure of spinal cord cultures to CDP-choline and THA distinctly reduced the development of typical apoptotic changes, whereas both necrotic and autophagocytic THA-induced MN injury occurred. These results indicate that CDP-choline treatment might exert a neuroprotective effect against neuronal apoptotic changes in a model of chronic excitotoxicity in vitro.