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NEUROPROTECTIVE EFFECT OF CITICOLINE

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Abstract: In recent years, citicoline has been the object of remarkable interest as a possible neuroprotectant. The aim of this study was to investigate if citicoline affected cell survival in primary retinal cultures and if it exerted neuroprotective activity in conditions modeling retinal neurodegeneration. Primary retinal cultures, obtained from rat embryos, were first treated with increasing concentrations of citicoline (up to 1000 μM) and analyzed in terms of apoptosis and caspase activation and characterized by immunocytochemistry to identify neuronal and glial cells. Subsequently, excitotoxic concentration of glutamate or High Glucose-containing cell culture medium (HG) was administered as well-known conditions modeling neurodegeneration. Glutamate or HG treatments were performed in the presence or not of citicoline. Neuronal degeneration was evaluated in terms of apoptosis and loss of synapses. The results showed that citicoline did not cause any damage to the retinal neuroglial population up to 1000 μM. At the concentration of 100 μM, it was able to counteract neuronal cell damage both in glutamate- and HG-treated retinal cultures by decreasing proapoptotic effects and contrasting synapse loss. These data confirm that citicoline can efficiently exert a neuroprotective activity. In addition, the results suggest that primary retinal cultures, under conditions inducing neurodegeneration, may represent a useful system to investigate citicoline neuroprotective mechanisms. Cytidine-5′-diphosphocholine (citicoline or CDP-choline), an intermediate in the biosynthesis of phosphatidylcholine (PtdCho), has shown beneficial effects in a number of CNS injury models and pathological conditions of the brain. Citicoline improved the outcome in several phase-III clinical trials of stroke, but provided inconclusive results in recent clinical trials. The therapeutic action of citicoline is thought to be caused by stimulation of PtdCho synthesis in the injured brain, although the experimental evidence for this is limited. This review attempts to shed some light on the properties of citicoline that are responsible for its effectiveness. Our studies in transient cerebral ischemia suggest that citicoline might enhance reconstruction (synthesis) of PtdCho and sphingomyelin, but could act by inhibiting the destructive processes (activation of phospholipases). Citicoline neuroprotection mayinclude: (i) preserving cardiolipin (an exclusive inner mitochondrial membrane component) and sphingomyelin; (ii) preserving the arachidonic acid content of PtdCho and phosphatidylethanolamine; (iii) partially restoring PtdCho levels; (iv) stimulating glutathione synthesis and glutathione reductase activity; (v) attenuating lipid peroxidation; and (vi) restoring Na+/K+-ATPase activity. These observed effects of citicoline could be explained by the attenuation of phospholipase A2 activation. Based on these findings, a singular unifying mechanism has been hypothesized. Citicoline also provides choline for synthesis of neurotransmitter acetylcholine, stimulation of tyrosine hydroxylase activity and dopamine release. Citicoline (cytidine-5′-diphosphocholine) is a neuroprotective agent that is administered following ischemic and traumatic brain injuries. There is little information about the antiseizure and anxiolytic effects of citicoline, which are therefore addressed in the present study. For evaluating the anticonvulsant effect of citicoline in the pentylentetrazole seizure model, a single intraperitoneal dose of citicoline was administered at 50, 100 or 150 mg/kg. Sedative and anxiolytic effects of citicoline were examined via elevated plus maze

and pentobarbital induced sleep tests. Results show that citicoline at the doses of 100 and 150 mg/kg significantly delayed the latent period compared with the control (P<0.05). Citicoline at the doses of 100 and 150 mg/kg significantly decreased total locomotion compared with the control (P<0.05). Additionally, citicoline at the doses of 100 and 150 mg/kg significantly increased both percentage of entry and time spent in the open arms in the elevated plus maze test (P<0.05). The pentobarbital induced sleep test showed that citicoline significantly reduced the latency to sleep (P<0.05). Our results suggest that acute administration of citicoline has anticonvulsant activity and sedative effect.

Key words: citicoline; glaucoma; excitotoxicity; apoptosis; diabetic retinopathy; primary retinal cultures; neuroprotection.

1. Introduction

Citicoline (cytidine-5′-diphosphocholine) is an essential precursor in the synthesis of phosphatidylcholine, a component of cell membranes. Several experimental studies *in vitro* and *in vivo* have suggested that citicoline is neuroprotective. In particular, citicoline has been found to efficiently counteract neuronal cell damage in animal models of cerebral ischemia [**1**]. In human studies, recent data suggest that administration of citicoline may slow down certain neurodegenerative diseases. In mild vascular cognitive impairment, oral citicoline significantly improved the Mini-Mental State Examination score and favorably influenced patients' mood [**2**]. In addition, in sub-acute ischaemic cerebrovascular disease, administration of citicoline has been found to improve functional rehabilitation and reduce the burden of care [**3**].

Fewer studies have investigated on the possible use of citicoline in the treatment of neurodegenerative diseases of the retina. Citicoline administration may efficiently reduce signs of the disease in glaucoma, where the retina undergoes neurodegenerative changes. In glaucoma patients, oral or intramuscular administration of citicoline was associated with an improved retinal and visual pathway functions [**4**–**6**]. Moreover, in patients with progressive glaucoma, oral citicoline was recently found to slow down glaucomatous rates of progression [**7**].

Here we have tested citicoline neuroprotection *in vitro* in conditions relevant to neuroretinal degeneration: glutamate-induced excitotoxicity, which is considered of pathophysiological relevance in glaucoma, and High Glucose (HG)-induced neurotoxicity, characteristic of diabetic retinopathy. *In vitro*, citicoline has already been shown to protect against HG neurotoxicity in retinal explants [**8**]. In addition, it has proven efficient in preventing excitotoxic cell damage in cerebellar granule cells [**9**] and motor neurons [**10**]. The purpose of this study was to assess citicoline neuroprotective ability against both neurotoxic conditions *in vitro* using primary retinal cultures, which can differentiate *in vitro* to produce mature neurons and Müller glia. Our results support the use of this system as a valuable tool to investigate the neuroprotective mechanisms of probes, such as citicoline, relevant to retinal neurodegeneration.

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