

Review Article

Citicoline: A Potential Breakthrough in Cerebrovascular Disorder

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Abstract

Citicoline, CDP Choline or Cytidine diphosphocholine is a novel drug with a broad spectrum of benefits for condition associated with neurological dysfunction. Citicoline is an endogenous compound and an essential intermediate in the synthesis of phosphatidylcholine (cell membrane phospholipid). It is launched worldwide (outside of US and Canada only) as a drug for stroke and head injuries. It plays important roles in structural integrity, signaling of cell membrane and plays important role in human physiology. It supports the synthesis of Acetylcholine and Betaine, a methyl donor to generate phospholipids. Citicoline attenuates the production of free radicals in Ischemic condition and also stimulates the activity of glutathione reductase and has the ability to promote learning and improve cognitive impairment in Parkinson's and Alzheimer's disease. Citicoline administration reduces the severity of mental and motor deficits associated head injuries and supports eye health and mental health. Pharmacokinetics suggests that it is well absorbed and high bioavailable orally. A dose of 500mg to 2000 mg per day is an effective based on clinical trials and is safe for use in elderly population and pediatrics. It has the ability to improve phospholipid metabolism, with a consequent improvement in the deteriorated axonal flow of dopamine.

Keywords: Citicoline; Phosphatidylcholine; Betaine; Choline; Neurological dysfunction

Abbreviations

CDP: Cytidine Diphosphocholine; US: United States; GABA: Gamma Amino Butyric Acid; ATP: Adenosine Tri Phosphate; BBB: Blood Brain Barrier; NE: Nor Epinephrine; IM: Intra Muscular

Introduction

Citicoline is a mononucleotide which is composed of choline, cytosine, pyrophosphate and ribose. It is an essential intermediate in the synthesis of cell membrane phospholipids i.e. Phosphatidylcholine and Acetylcholine, a key neurotransmitter. Phospholipids are essential constituents of cell and have a high turnover rate, which requires a continuous synthesis of these compounds to ensure the adequate function of cell membrane [1,2]. Citicoline first identified in 1955 by Kennedy *et al.* and was synthesized in 1956. Initially it was developed in Japan to treat stroke patients. Later, Interneuron obtained its marketing and manufacturing license for Canada and US in 1993. By September 1997, a patent application had been filed by Interneuron worldwide, for the use of Citicoline [3]. It is widely available as an approved drug for the treatment of neurological disorder. When administered, Citicoline is hydrolyzed in the intestinal tract and in circulation to form choline and cytidine. Choline is a component of the diet and is produced in the brain in small amount. It plays several essential roles in human physiology, including signaling of cell membrane, support synthesis of betaine, a methyl donor and Acetylcholine. Studies in neuronally related cell lines have also shown that Cytidine administration increased the incorporation of choline into membrane phosphatidylcholine. Citicoline lowers the toxicity index an additional 20 fold and has low level of toxicological index

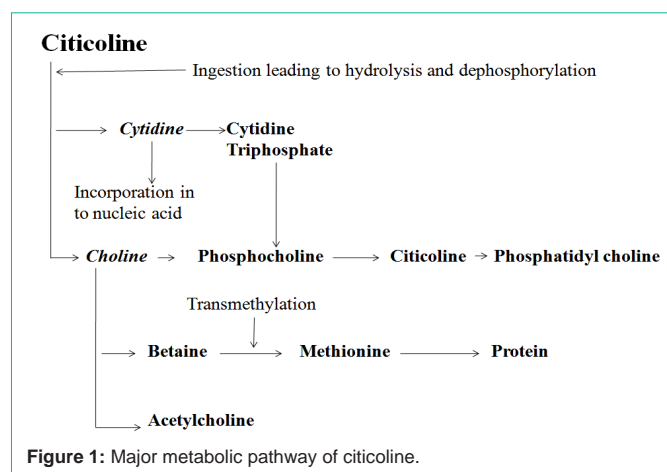
[4,5]. It prevents the accumulation of free fatty acids and generation of free radicals at the site of ischemia, thereby prevents the initiation of proinflammatory cascade of events. Citicoline has been shown to act as a dopaminergic agonist. In addition, it also has some effects upon the other monoamines, serotonin and nor epinephrine, muscarinic receptors, and glutamate and GABA [6]. It inhibit catabolism of cerebral phospholipids and has a protective effect upon membrane ATPase and enzymes involved in brain energy metabolism, particularly succinyl dehydrogenase and citrate synthetase [7-9].

Bioavailability / Pharmacokinetics

Administration of 300mg dose to healthy adults shows nearly complete absorption, with less than 1% of excretion in feces [10]. The main route of excretion was found to be via a respiratory route, with significant excretion occurring through urine. A confirmatory study, using radioactive Citicoline in rats, found 62.8% of total radioactivity distributed in brain tissues as phospholipids, including phosphatidylcholine and sphingomyelin. Metabolites of orally administered Citicoline resynthesize endogenous Citicoline, which yields beneficial effects for the synthesis and incorporation of neuronal phospholipids [11-13]. Only a small percentage of total Citicoline crosses the BBB as choline and Cytidine, the utilization of these precursors is extremely efficient [14].

Mechanism of Action

Citicoline has beneficial effects on neurological functions; it acts by increasing the synthesis of phosphatidylcholine, the primary neuronal phospholipid and enhancing the production



of acetylcholine [15]. Brain phospholipid synthesis is impaired following stroke and ischemic events. Oral citicoline administration increases the plasma levels of choline and cytidine, building blocks used to restore neuronal membrane integrity. Citicoline seems to have different effects on phosphatidylcholine synthesis in younger versus older adults. Phosphatidylcholine is an essential compound for cell membrane integrity and reduces in brain as a result of aging. Clinical data suggest that uridine and choline are the circulating substrates through which citicoline facilitates an increase in brain membrane phospholipid synthesis. Uridine crosses the blood-brain barrier and is converted to uridine triphosphate. Uridine directly gets converted to cytidine triphosphate intracellularly. The frontal lobe is the preferred site for the deposition of Citicoline [16-19].

This area of the brain contributes to memory function by supporting attention, memory capacity, and by reducing mental fatigue. Citicoline has benefit in patients experiencing ischemia by decreasing the accumulation of free fatty acids at the site of the lesion, which occurs as a result of neuronal cell damage and death. After the initiation of ischemia, there is a significant increase in arachidonic acid, glycerols, and free fatty acids caused by the breakdown of neuronal membranes (Figure 1) [20-22].

Toxic metabolites such as prostaglandins, thromboxanes, and free radicals get accumulated, leading to further damage. Intracerebral administration of citicoline prior to induction of ischemia reduces the rise in free fatty acids, arachidonic acid, and other toxic metabolites, attenuating free radical damage and restoring membrane function [23].

Citicoline normalizes neurotransmitter release pattern. In conditions of cerebral hypoxia and ischemia, NE (Nor Epinephrine) release may decrease, while the release of dopamine may increase. Citicoline administration to rats kept in a chronic hypoxic state reduces behavioral deteriorations and increased survival time. It is able to increase the dilation of blood vessels in animals with cerebral microcirculation injury, significantly increasing cerebral blood flow. Citicoline administration to rats increases striatal dopamine synthesis lesions and have shown to regenerate nerve cells. Citicoline enhances the preservation of an inner mitochondrial membrane component known as cardiolipin, which is an important regulatory factor for preservation of mitochondrial function [24-27]. It also facilitates the preservation of sphingomyelin, which promotes signal transduction

in nerve cells and attenuates lipid peroxidation. It has been shown to have direct free-radical suppressive effects. Citicoline treatment significantly increases the length and branch points of dendrites, increasing the overall surface area occupied by neurons, which leads to an increased efficiency of sensory information processing [28-31].

Clinical Applications

Citicoline serves as a precursor for neuronal membrane phospholipids and an important nutritional substance for supporting learning ability and memory functions [32]. Neuroprotection of citicoline has been described since 1978 and several mechanism of action has been proposed [33]. Citicoline pre-treatment prevents excitotoxic death caused by excessive glutamate exposure in an *in vivo* focal cerebral ischemia model [34]. Experiments in animals and humans provide evidence of its ability to promote these important cognitive processes. Citicoline at a dosage of 1,000 mg/day for 30 days is very effective in Alzheimer's disease, traumatic brain injury and vascular dementia [35]. It enhances cholinergic neural transmission, activate repair mechanisms to rejuvenate neuronal membranes and has regulatory effect on parameters associated with blood flow and circulation. It has been found that citicoline have moderate antidepressant effect in patients with Alzheimer's disease and multi-infarct dementia. Citicoline has been reported to decrease infarct volume by 27.8% and to reduce brain edema with either a single therapy or combination with other agent like nimodipine [36].

Citicoline at a dosage of 1,000mg/day for 15 days, followed by 500 mg/day, has benefits in Parkinson's disease. Levodopa is used in the long-term management of Parkinson's disease; however, prolonged use of levodopa decreases efficacy and the development of dyskinesia. Citicoline has been found to have a levodopa-sparing effect and an ability to increase dopamine synthesis. 1000 mg/day IM dose of citicoline for 15 days show beneficial effects on eye health, specifically in cases of amblyopia and glaucoma [37-39]. It has been considered for the treatment of cocaine dependence because of its ability to repair neuronal membranes, which are damaged by cocaine use, and its ability to increase central nervous system dopamine levels [40]. Citicoline play as an adjunctive therapeutic agent for the treatment of disease arising from an infectious etiology including sequelae of sepsis, parasitic infection such as cerebral malaria by deregulating the host immune response. It has the ability to enhance cognitive function at 2,000 mg/day for 6 weeks [41].

Conclusion

Citicoline is a novel compound with a very broad spectrum of benefits in conditions associated with symptoms of neurological dysfunction. It maintains neural health and optimal cognitive function. Citicoline promotes cholinergic and dopaminergic functions and supports phospholipid synthesis and incorporation into cell membranes. Citicoline also enhances antioxidant mechanisms in the body, while suppressing the damaging effects of free radicals on neural tissue. It also promotes anti-inflammatory activities and optimizes patterns associated with the release of neurotransmitters. Given its widespread activity on neural tissue, citicoline is considered as a comprehensive therapeutic agent for supporting brain health [42-44]. Citicoline has no adverse events. Minor transient adverse effects are rare and most commonly include stomach pain and diarrhea [45].

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