Choline alphoscerate pharmacology and its role in the treatment of cognitive impairment related to neurological disorders

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Summary

Dementia diseases are continuously increasing, with a prevalence of 4/6 million of new cases per year worldwide. The majority of patients live in developed countries, where survival into old age is quite common. However, the forecast growth rate of dementia patients is three times higher in India, China and neighboring countries in South Asia and the Western Pacific. Modulation of acetylcholine neurotransmission is a therapeutic approach to dementia when the cholinergic neurons do not present major damage. The different molecules used to enhance central cholinergic tone are: cholinergic precursors, acetylcholine esterase inhibitors, nicotinic receptor agonists and M2 receptor antagonists. Among the cholinergic precursors, the semi-synthetic compound choline alphoscerate has emerged as a valid therapeutic approach for the treatment of cognitive impairment in neurological patients. Several studies have shown that choline alphoscerate is able to increase the synthesis and the release of acetylcholine in patients with Alzheimer-related dementia, cerebrovascular damage and aging. Moreover, preliminary evaluations suggest a useful role for choline alphoscerate in patients with cognitive impairment of varying severity related to brain trauma or to Parkinson’s disease. Literature data suggest that, in these conditions, choline alphoscerate shows a better efficacy than other cholinergic precursors (choline, lecithin, phosphatidylserine and citicoline) and also has a good tolerability and safety profile. In adult-onset dementia, it could be a therapeutic resource, either in association with the newer acetylcholine esterase inhibitors or as a monotherapy in patients in whom these inhibitors are not tolerated or are contraindicated.

KEY WORDS: choline alphoscerate, citicoline, cholinergic system, cognitive dysfunction, dementia

Introduction

Acetylcholine is widely distributed in the nervous system and has been implicated as playing a critical role in cerebral cortical development, cortical activity, cerebral blood flow control, and the sleep-wake cycle, as well as in the modulation of cognitive performances and learning and memory processes (1-3). The basal forebrain cholinergic neurons (i.e. those localized in the medial septum, horizontal and vertical diagonal band of Broca, and nucleus basalis of Meynert) provide the major cholinergic projections to the cerebral cortex and hippocampus and have been described to undergo moderate degenerative changes during aging, resulting in cholinergic hypofunction that has been linked to the progressive memory impairment related to aging (4,5). The age-dependent degeneration of basal forebrain cholinergic neurons might be due to a decrease in trophic support, even though an attenuation of neurotrophic signaling (i.e. nerve growth factor) in sensory neurons has been observed in aging (6). However, the functional decline associated with aging observed across species does not primarily result from cell loss, but from other mechanisms, including reductions in gene expression and impairments in intracellular signaling and in cytoskeletal transport, which may mediate cholinergic cell atrophy leading to age-related functional decline in the brain (7-10).

Previously it has been documented that enhancement of cholinergic neurotransmission can counteract the impairment of cognitive functions related to aging or degenerative brain diseases (11). Several drugs may be used to enhance cholinergic neurotransmission, e.g. acetylcholinesterase inhibitors and choline precursors (such as choline, lecithin, citicoline and choline alphoscerate) which, freely crossing the blood brain barrier, can be used for the synthesis of acetylcholine and membrane phospholipids in neuronal cells.

The rationale for the use of acetylcholinesterase or cholinesterase inhibitors in the treatment of adult-onset dementia disorders lies in their capacity to increase the synaptic availability of acetylcholine by delaying its catabolism (12). However, the efficacy of both inhibitors in the treatment of adult-onset dementia disorders is related to the presence of adequate central cholinergic tone. In fact, the grade of the disease and the loss of cerebral cortical cholinergic synapses may reduce the efficacy of these drugs in the treatment of cognitive impairment. By contrast, postsynaptic muscarinic receptors are preserved in several dementia disorders (e.g. Alzheimer’s disease) and their stimulation may contribute to maintaining reasonable levels of brain cholinergic function in spite of loss of cholinergic synapses (13). Clinical trials using first-generation acetylcholine precursors, i.e., choline and phosphatidylcholine (lecithin), failed to document efficacy in the treatment of patients with dementia (whether the drugs were used as
monotherapy or in combination with cholinesterase inhibitors). This was probably because they were able to increase brain acetylcholine contents but did not stimulate acetylcholine release, and because they penetrate the blood-brain barrier poorly (12,14).

Second-generation agents (choline alphoscerate, citicoline) do not present this disadvantage. In the body, choline alphoscerate is split into choline and glycerophosphate. Due to a rapid increase in plasma concentration, but also thanks to its electrical neutrality, choline released by the scission of choline alphoscerate penetrates the blood-brain barrier and becomes involved in acetylcholine synthesis in the brain. This results in increased cholinergic activity because of increases in acetylcholine synthesis and release (14).

Choline alphoscerate is a precursor in the biosynthesis of brain phospholipids (15) able to increase the bioavailability of acetylcholine in nervous tissue (16) and to counter age-related brain microanatomical changes (17). Moreover, it is also able to improve cognitive function in dementia disorders of neurodegenerative or vascular origin (18-20).

The pharmacology of choline alphoscerate

L-alpha-glycerylphosphorylcholine, also called choline alphoscerate, is a phospholipid metabolite with the following structural formula:

After oral administration of choline alphoscerate (1200 mg) in healthy young volunteers, mean free plasma choline increased quickly (from 10.1±0.66 µM/L at 0 h to 13.6±1.04 µM/L at 2 h); the Cmax was reached in about 3 hours (14.2±1.66 µM/L) and the values recorded remained higher than basal for about 10 hours (21).

After oral administration, choline alphoscerate is cleaved within gut mucosal cells, by the action of glycerylphosphorylcholine diesterase (L-3-glyceryl-phosphorylcholine glycero-phosphohydrolase), (22) into glycerylphosphate and free choline, which enters the portal circulation and can reach brain tissues, where it is incorporated into the phospholipid fraction of the neuronal plasma membrane and into microsomes (23). In the brain, the concentration of choline alphoscerate increases slowly and attains maximum levels 8 hours after administration, thereafter remaining constant over 30 hours (24).

Intramuscular administration

Clinical studies performed in 12 normal volunteers aged 20-29 years documented a significant rapid increase in plasma choline levels after intramuscular injection of choline alphoscerate (1000 mg) (from 9.7±0.6 mcmol/L before administration to 35.5±3.5 mcmol/L 0.25 h after administration, p<0.01), which thereafter decreased over about 6 hours (25). In the same group of patients, the administration of citicoline (1000 mg) (an acetylcholine precursor) was associated with a rapid increase in plasma choline (from 11.2±0.6 mcmol/L before administration to 24.3±1.5 mcmol/L 0.25 h hour after administration, p<0.01), with a subsequent decrease in plasma levels over about 4 hours. The analysis of these data showed that administration of choline alphoscerate (1000 mg) induced, after 0.25 h, significantly higher levels of plasma choline with respect to the administration of citicoline (1000 mg) (p<0.05), followed by a very slow decline in choline plasma values (6 h for choline alphoscerate, 4 h for citicoline).

Analysis of the pharmacokinetic parameters obtained in these patients showed no significant differences between choline alphoscerate and citicoline in time to peak plasma values (Tmax) or in plasma half-life (choline alphoscerate: Tmax: 0.5±0.1 h; plasma half-life: 1.37±0.26 h; citicoline: Tmax: 0.4±0.1h; plasma half-life: 2.18±0.50 h). By contrast, both the peak concentration (Cmax) and the area under curve (AUC) values were significantly higher for choline alphoscerate (25) (Figure 1).

Intravenous administration

Intravenous administration of choline alphoscerate in young volunteers induced a rapid increase in choline plasma levels after 30 minutes with the following pharmacokinetic values: AUC 66.67 µMol/h/L, Tmax 0.08 hours and Cmax 163.94 µMol/L (Table I) (21).

Mechanism of action

Choline alphoscerate is involved in brain phospholipid metabolism, being cleaved by the enzyme glycerylphosphorylcholine diesterase into a molecule of choline and another of glycerol-1-phosphate. Choline can be used for synthesizing acetylcholine whereas glycerol-1-phosphate, after phosphorylation, can enter the phospholipid pool (22,26). Activation of these pathways could provide...
both free choline and phospholipids for synthesizing acetylcholine and reconstituting nerve cell membrane components. On the other hand, both choline kinase and phosphocholine acetyltransferase are able to covert choline into phospholipids. Choline alphoscerate is therefore a source of choline of the same form that a cell would obtain scavenging its own membranes and probably the form of choline that neurons use for synthesizing acetylcholine when larger amounts of choline are required, or when it is poorly available (27).

**Clinical implications**

**Alzheimer’s disease**

Cholinergic function changes are strongly implicated in the pathogenesis of learning and memory impairment in dementia disorders including Alzheimer’s disease (1,28,29). A primary trait of Alzheimer’s disease is the degeneration of basal forebrain cholinergic neurons, which causes a remarkable deficit of pathways of corticoncholinergic neurotransmission, such as acetylcholine synthesis, release, and uptake, and choline acetyltransferase and acetylcholinesterase activities (2,30). Therefore, the first attempts to treat Alzheimer’s disease pharmacologically considered the use of cholinergic-enhancing drugs (i.e. choline acetyltransferase and acetylcholinesterase inhibitors and acetylcholine precursors). Among the cholinergic precursors assessed for the treatment of adult-onset cognitive decline, choline alphoscerate is probably one of the most effective in increasing acetylcholine bioavailability (16). In a multicenter double-bind randomized placebo controlled trial performed in 261 patients with degenerative mild-to-moderate Alzheimer’s dementia, treatment with choline alphoscerate (1200 mg/day for 180 days) significantly slowed the cognitive decline, with an improvement of 4-7 points in the Alzheimer’s Disease Assessment Scale-Cognitive Subscale score at the end of the treatment. Moreover, patients treated with choline alphoscerate showed improvements of all symptoms, as evaluated using the Mini-Mental State Examination, Global Deterioration Scale, Alzheimer’s Disease Assessment Scale-Behavioral Subscale, Alzheimer’s Disease Assessment Scale, and Clinical Global Impression scale, after 90 and 180 days versus baseline, whereas in the placebo group these symptoms remained unchanged or worsened (20). An experimental study performed in adult male Wistar rats revealed that the association of choline alphoscerate with rivastigmine dose-dependently increased both acetylcholine levels and [3H]hemicholinium-3 binding; these effects were slightly more pronounced in the hippocampus than in the frontal cortex or striatum. By contrast, administration of choline did not potentiate the effects of rivastigmine (31). These results are in agreement with a previous experimental study which showed that the concomitant administration of choline alphoscerate and a rivastigmine dose four-fold lower than the ED50 increased acetylcholine levels and immunoreactivity, this increase being more pronounced in the hippocampus, an area related to learning and memory (32). The advantage of the proposed association, compared with cholinesterase inhibitor monotherapy, lies in the lower doses of cholinesterase inhibitor needed to increase brain levels of acetylcholine. This aspect may also be useful for reducing the probability of side effects or toxic effects (primarily gastrointestinal and hepatic) induced by cholinesterase inhibitors (33). Another potential advantage of the association could be the ability to make available larger amounts of choline and consequently of acetylcholine in patients in whom cholinesterase inhibition may be not effective due to low levels of neurotransmitter in cholinergic synapses (31).

**Cerebrovascular disorders and vascular dementia**

The basal forebrain cholinergic system plays an important role in cognitive function, particularly in the domains of attention, memory and emotion; it is also involved in cerebral blood flow control (34). Cholinergic structures and specific brain areas such as the hippocampus (i.e. CA1 neurons) are particularly sensitive to ischemic damage (35). This may account for a role of impaired cholinergic neurotransmission in the pathophysiology of vascular dementia (VaD), which is the second most common form of adult-onset dementia after Alzheimer’s disease (36). Experimental studies in spontaneously hypertensive rat (SHRs) and stroke-prone SHRs (SP-SHRs) described significant reductions in cholinergic markers in the neocortex, hippocampus and cerebral spinal fluid (37-39). No drugs are licensed for symptomatic relief of the cognitive symptoms of VaD; indeed, data on the benefits produced in cognition domains by acetylcholinesterase/cholinesterase inhibitors and memantine are inconclusive (40). However, even though there are no specific drugs for the treatment of VaD patients, it is possible that both acetylcholinesterase/cholinesterase inhibitors and cholinergic precursors may be useful in this population. Previously, it has been hypothesized that both acetylcholinesterase/cholinesterase inhibitors (i.e. tacrine,
donepezil, rivastigmine and galantamine) and memantine can induce a neuroprotective action, by countering glutamate neurotoxicity via alpha-4-beta-2 and alpha-7 nicotinic acetylcholine receptors and by inhibiting apoptosis (41).

Several studies have reported that choline alphoscerate, by increasing acetylcholine release in rat hippocampus, is able to improve memory and attention, as well as affective and somatic symptoms (fatigue, vertigo) in VaD patients (14). In agreement with this, experimental studies have documented that treatment with choline alphoscerate countered nerve cell loss and the glial reaction primarily in the CA1 subfields and in the dentate gyrus of the hippocampus of SHRs, while phosphatidylcholine did not affect hypertension-dependent changes in hippocampal microanatomy (42).

Recently, in spontaneously hypertensive rats, Tayebati et al. (43) documented that the coadministration of the galantamine with choline alphoscerate elicits neuroprotective effects superior to those observed with single compounds. This synergism is probably due to a neuroprotective activity of galantamine probably related to up-regulation of the protective protein Bcl-2, mediated by alpha-7 nAChR, as well as to the enhanced release of acetylcholine induced by choline alphoscerate. Indeed, choline alphoscerate was shown to counter both hypertension-related nerve cell loss in the hippocampus and the glial reaction in this key area for learning and memory (42). Moreover, the increase in cholinergic neurotransmission induced by choline alphoscerate, may prevent glutamate neurotoxicity via activation of nicotinic acetylcholine receptors and the phosphatidylinositol 3-kinase cascade (41).

In all clinical trials, treatment with choline alphoscerate improved cognitive symptoms (such as disorientation, irritability, emotional lability, and indifference to surroundings), as documented by the decreased mean Sandoz Clinical Assessment Geriatric score (18). Compared with citicoline (1000 mg i.m.), choline alphoscerate (1000 mg i.m.) was found to have a more favourable impact on the Sandoz Clinical Assessment Geriatric score (18). Moreover, in acute cerebrovascular diseases (e.g. stroke), treatment with choline alphoscerate (1000 mg/day i.v. for 4 weeks followed by 1200 mg/day for 5 months) induced a marked improvement in neurological functions as documented through the Mini-Mental State Examination, Global Deterioration Scale and Crichton Geriatric Rating Scale assessments (44-46).

Parkinson’s disease

The presence of dementia has been reported in about 80% of patients with Parkinson’s disease (47-49), in whom it is responsible for increased mortality and decreased efficacy of antiparkinsonism treatment. Cholinesterase inhibitors, particularly rivastigmine, and memantine, a partial agonist of glutamate receptors, have been shown to be effective in patients with Parkinson’s disease and dementia even though this efficacy can only be regarded as moderate (50,51).

Moreover, there is no evidence for the long-term efficacy of these agents at the stage of moderate cognitive disturbance. On the other hand, in view of the impairment of the ascending cholinergic system that develops in the early stages of Parkinson’s disease due to degeneration of neurons in the basal nucleus of Meynert, and the role it plays in the development of the cognitive deficit, it is reasonable to hypothesize a role for acetylcholine precursors in the management of dementia in these patients. Levin and coworkers, in a recent open 10-day pilot study, recruited 60 Parkinson’s disease patients with cognitive impairments of varying severity in order to compare the effects of piracetam (2000 mg, i.v.) with those of choline alphoscerate (1000 mg, i.v.) on the cognitive impairments (52). In this study, the authors demonstrated that choline alphoscerate was quite effective and safe in Parkinson’s disease patients with cognitive impairments. In particular they documented that choline alphoscerate produced marked and moderate improvements in the state of cognitive functions in significantly larger proportions of patients than did piracetam (40% and 25%, respectively; p<0.01). Indeed, in patients with PD, the patients’ general status and quality of life were better in patients receiving choline alphoscerate than in those given piracetam. Side effects were described in 15% of patients treated with choline alphoscerate and in 35% of those receiving piracetam. However, these effects were mild and did not require treatment withdrawal (52).

The higher efficacy of choline alphoscerate may be related to the observed increased in cholinergic neurotransmission in the frontal cortex and limbic system (50). However, even though, theoretically, the increase in cholinergic neurotransmission could increase the parkinsonism symptoms related to the disinhibition of striatal cholinergic neurons, no increase in motor deterioration in patients with Parkinson’s disease was described during choline alphoscerate treatment (52).

Traumatic brain injury

Traumatic brain injury (TBI) is a complex injury associated with a broad spectrum of symptoms and disabilities (53). In a recent experimental study, the presence of a common pathophysiological mechanism in TBI that causes a loss of alpha7 nicotinic receptor able to induce excitotoxic damage, inflammation and cognitive impairment after brain injury, was clearly described (54). Bansal and coworkers have also postulated that the vagal cholinergic system might be capable of decreasing post-TBI inflammation probably through a secondary mediator (i.e. ghrelin) (55).

Therefore, it is possible that cholinergic stimulation may be capable of reversing the inflammation during TBI. Indeed, previously, Mandat and coworkers evaluated the effect of choline alphoscerate (1000 mg/day i.m. for 14 days, then 800 mg/day orally for the next 28 days) in patients with acute cerebral trauma and documented, after 3 months, an improvement in neurological conditions in about 96% of the patients, without the development of side effects (56).

On the basis of these findings, the authors hypothesized a role for choline alphoscerate in patients with cranial injury. However, since this is the only study reporting these data, further studies may be required in order to evaluate fully the role of acetylcholine precursors in the management of cranial injury.
Cognitive function

Normal and pathological aging is accompanied by impairment of short-term memory. Acetylcholine is the neurotransmitter most involved, in different ways, in all memory systems (57-59).

Deficient functioning of basal forebrain cholinergic neurons plays a role in the pathophysiology of loss of working memory (60,61). This is underpinned by a loss of brain cholinergic neurons, reduced synthesis and release of acetylcholine, as well as by impaired function of brain cholinergic receptors (62).

The observation that the administration of scopolamine (a muscarinic antagonist) to healthy young subjects induced a cognitive impairment resembling that found in adult-onset dementia (63), and also the finding of reduced activity of choline acetyltransferase in the cerebral cortex and hippocampus of patients affected by Alzheimer’s disease, contributed to the development of the cholinergic hypothesis of geriatric memory dysfunction (64).

Experimental and clinical studies have documented that choline alphoscerate is able to counter the amnesia induced by the cholinergic muscarinic receptor antagonist scopolamine (65-67), but it is not able to improve the amnesic effect induced by lorazepam (a benzodiazepine) in healthy patients, showing that the effect of choline alphoscerate is selective on cholinergic neurotransmission (68).

Moreover, choline alphoscerate is also able to improve the age-related decline of both the synthesis and the release of growth hormone (GH) (69,70).

Growth hormone decline is related to cognitive impairment in the elderly (71) and the cholinergic system is an important part of mechanisms regulating GH release stimulated by growth hormone-releasing hormone (GHRH) (72). GHRH is the hypothalamic hormone that triggers secretion of GH from the pituitary. The observation that choline alphoscerate (71) reduced the age-related decline in GH responsiveness to GHRH further strengthens the hypothesis of cholinergic activity of this compound. The interference with mechanisms of GH release suggests that choline alphoscerate may also be considered for other indications, besides the most documented ones in the cognitive domains (Figure 2).

A recent experimental study investigated the effects of cytidine-5’-diphosphocholine (citicoline, 325 mg/kg/day) and choline alphoscerate (150 mg/kg/day) on vesicular acetylcholine transporter, choline transporter and acetylcholine concentrations in the rat frontal cortex, striatum and cerebellum (27). The authors documented through Western Blot analysis that both citicoline and choline alphoscerate increased the vesicular acetylcholine transporter expression in the frontal cortex, striatum and cerebellum versus control, while they did not modify choline transporter expression. By contrast, the ELISA test revealed that choline alphoscerate but not citicoline increased the vesicular acetylcholine transporter concentration in the frontal cortex, supporting the view that choline alphoscerate probably represents, among those investigated to date, the choline-containing phospholipid with the highest activity on the cholinergic machinery (27).

Finally, the treatment with choline alphoscerate was associated with a low incidence of adverse reactions and no changes in heart rate. In view of the good effectiveness/safety profile of choline alphoscerate, this compound may be considered as an option in older adults with dementia at risk of cardiovascular events (74).

Concluding remarks

Literature data document that, among the choline-containing phospholipids, choline alphoscerate is probably the most effective in enhancing in vivo acetylcholine release. It has also shown positive results in the cognitive domain in patients with different diseases, such as mild-to-moderate dementia induced by neurodegenerative, vascular or combined disorders, and cognitive impairment in Parkinson’s disease and brain trauma.

Various clinical and experimental data show that choline alphoscerate is able to improve cognitive symptoms (memory and attention) with higher efficacy with respect to other cholinergic precursors (in particular, citicoline) and has a good tolerability profile. Therefore, in view both of its clinical efficacy and its low side effects, choline alphoscerate is a good therapeutic choice in patients with dementia related to neurological diseases.

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