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Citicoline: A Food That May Improve Memory

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Attempts to improve memory function with drugs affecting the brain have given unimpressive results. Dietary supplements are more widely available, and there also has been little evidence of their positive effect on memory. Citicoline may be a valuable exception. In several countries it has been registered as a nootropic drug for decades, but recently it did not prove effective in treatment of acute ischemic strokes and brain injuries. In the USA, citicoline attained the status of "generally recognized as safe", and in the European Union recently it was qualified as a "novel food". Small randomized, placebo-controlled trials involving healthy volunteers revealed that permissible doses of this novel food produce positive effects in the human brain recognized electrophysiologically, neurochemically, and functionally. Citicoline supplementation may be useful for subjects with memory disorders of mild-to-moderate intensity, those undergoing neurorehabilitation following brain strokes, and for healthy subjects facing requirements for enhanced attention and mental effort.

MeSH Keywords: Dietary Supplements • Memory Disorders • Nootropic Agents

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Background

Memory disorders commonly occur in the elderly but they also may appear in younger people. It is commonly believed that so-called memory lapses (forgetfulness) are the first symptoms of dementia. Fortunately, in most cases they have a different cause [1].

Almost everybody will experience certain deterioration of memory with age. This is manifested as the above-mentioned forgetfulness but also as prolongation of time required to memorize new information and to recall information previously remembered. Cognitive functions are slowed but not impaired. Progression and a characteristic picture of memory disorders is the evidence of a syndrome called mild cognitive impairment (MCI). In comparison with healthy subjects of similar age, persons suffering from MCI reveal inferior abilities regarding short-term memory. Disturbances mainly concern recalling recent events, while memory of remote events is usually well preserved. MCI is often (but not always) a transitory stage between normal ageing and dementia. The yearly incidence of dementia among MCI patients is estimated as 3% to 17% [2]. Dementia is characterized by most severe memory dysfunction, usually associated with concurrent neuropsychiatric symptoms; it is a life-threatening problem with serious social and medical consequences. However, the issue of dementia is beyond the scope of the present review.

Treatment of initial memory disorders is a controversial issue. While there seems to be agreement in the contemporary scientific literature that MCI is a pathologic condition that requires drug therapy, forgetfulness is not a disease. Moreover, few if any drugs or food supplements proved useful in this setting. Citicoline, recently qualified as a new food in the European Union, may be a valuable exception.

Search Strategy and Selection Criteria

References for this review were selected through PubMed, Web of Science, and Scopus databases as follows: For general remarks on the issue of pharmacotherapy of memory disorders, few representative reviews and metaanalyses published since 2009 were chosen from those identified through searches of by the use of terms "memory" and "pharmacotherapy". To illustrate the evolution of citicoline from a prescription drug to a novel food, and to review studies published to date on the subject of citicoline and memory, the aforementioned databases were thoroughly reviewed for relevant papers using the terms "CDP-choline" and its variants ("CDPcholine", "cytidinediphosphocholine", etc.), and "citicoline".

Pharmacotherapy of Memory Disorders

In the Anatomical Therapeutic Chemical classification of drugs (ATC), most medicines indicated to treat memory disorders belong to group N 06 B: psychostimulants and nootropics. This group includes substances with various chemical structures, which common feature is ability to activate central nervous system metabolism. Here we encounter centrally acting sympathomimetics such as amphetamine or pemoline, but also xanthine derivatives such as caffeine which is actually a food product. Subgroup N 06 BX contains "other medicines", with piracetam and vinpocetine as the majors.

Safety and efficacy of nootropics in pharmacotherapy of memory disorders is controversial. Some of them (amphetamine, methamphetamine and methylphenidate) should not be used due to the risk of causing not only serious behavioral, but also structural and neurochemical changes [3]. Others are known to stimulate metabolic processes in the brain, but do not significantly improve memory and cognitive processes. Piracetam, which pharmacological activity is associated, *inter alia*, with an improvement in functioning of mitochondria in the central nervous system [4], has only a slight positive effect on memory disorders [5]. Vinpocetine, which stimulates cerebral circulation, glucose consumption and ATP production, is sometimes advertised as medicine improving memory. There is no scientific data, however, to confirm such effects of this drug [6].

There have been attempts to treat MCI with agents belonging to group N 06 D, i.e. anti-dementia drugs, but also without much success. Russ & Morling [7] and Trico et al. [2] presented meta-analyses of clinical trials on the efficacy of rivastigmine, donepezil and galantamine – cholinesterase inhibitors which increase acetylcholine concentration in the brain, and memantine – NMDA receptor antagonist. The results were negative, no clinically significant improvement in memory or cognitive functions were observed.

The most popular, and at the same time considered the safest memory enhancer is another drug of group N 06 D, i.e. *Gingko biloba* extract. In ancient times, *Gingko* seeds were recommended by traditional Chinese medicine for numerous diseases including those of elderly people. In Europe, standardized *Gingko* leaf extract was first used in 1965 to treat cerebral and peripheral circulation insufficiency [8]. This product, EGb761, is a composite medicine containing numerous pharmacologically active substances, e.g. flavonoids and terpenoids. Its efficacy in various neurological diseases, including memory disorders of different intensity, was assessed in numerous randomized clinical trials. The drug was used at the doses from 80 to 720 mg daily for the period ranging from 2 weeks to 2 years and the results were in many cases moderately positive [9]. However, the largest randomized trial, conducted in 2000–2008 in the

USA and involving 3,000 subjects aged over 72 without symptoms of dementia, where the median follow-up was 6 years, gave a negative result [10].

Cosmetic Neurology: from Illegal Medicines to Dietary Supplements

Since forgetfulness is not considered a pathologic condition but rather a dysfunction, the use of medicines improving memory in forgetful subjects is a controversial issue. This is part of a wider problem of approving the use of drugs and substances which reinforce ("improve") cognitive and memory functions by healthy subjects. Such medicines are called "cognitive enhancers" or "smart drugs". One of the initiators of a serious discussion on this subject is Anjan Chatterjee, who coined the term "cosmetic neurology" to describe the use of cognitive enhancers to improve memory and cognitive functions in healthy people. Cosmetic neurology would be a field of medicine analogical to "cosmetic surgery", which task is not to cure diseases or correct disabilities – this is the domain of "plastic surgery" – but to "improve" and "beautify" people with normal, age-adequate appearance. Development of cosmetic neurology, although problematic from the ethical point of view, is according to Chatterjee unavoidable. One of the reasons is that pharmaceutical companies are seeking to reach a wider group of subjects, including healthy ones – which is actually already happening in other fields of medicine. One example is proton pump inhibitors, which are advertised to healthy people as a simple way to avoid heartburn following ingestion of heavy food, such as e.g. pizza pepperoni [11].

At the background of the discussion on the use of cognitive enhancers by subjects considered healthy is the issue of availability of these substances. Some nootropics are no longer used in medicine or their use is marginal, so that they are available only illegally. One example is the infamous (and not without a reason) amphetamine, which in the ATC classification is listed in the group of centrally acting sympathomimetics (ATC N06 BA) and is still used as the drug in treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy [12]. Others, such as the above-mentioned vinpocetine, are prescription drugs despite strong efforts of manufacturers to obtain authorization for non-prescription availability. Still others, widely used and considered safe, are already available over the counter and in some countries have obtained the status of dietary supplements. An example is *Gingko biloba* extract. Another example is piracetam, which still is a prescription drug in Poland, but in the USA since 2006 it had been temporarily sold as a food supplement, until 4 years later FDA "discovered" that it does not meet the supplement definition [13].

This last example provokes a question about what exactly are food supplements, alternatively called dietary supplements. The literature on this subject is abundant. To mention just the two authoritative sources, I will recall the definition included in the Encyclopaedia Britannica [14] according to which a dietary supplement is any vitamin, mineral, herbal product, or other ingestible preparation that is added to the diet to benefit health. Dietary supplements must be at the same time differentiated from medicines and from food. I will also quote the definition found on the website of the European Union [15], according to which dietary supplements are concentrated sources of nutrients or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet. They are marketed in "dose" forms, i.e. as pills, tablets, capsules, liquids in measured doses etc. Common rules for all the countries of the European Union were introduced by the Directive 2002/46/EC of the European Parliament and Council on the approximation of the laws of Member States relating to food supplements. This directive established harmonized rules for introducing food supplements to the EU market, which are as follows: Agents already present on the market remain to be dietary supplements in EU, but new substances, called "novel food", must undergo a detailed procedure of safety assessment conducted by the European Food Safety Authority (EFSA) located in Parma (Italy). There is nothing strange in such a procedure, since food has to be truly safe.

Can food supplements be effective in correcting disorders and slowing down memory loss? About 10 years ago McDaniel et al. [16] summarized scientific data on this subject, taking into account mainly the results of randomized trials. The items discussed included both xenobiotics to human body: piracetam, vinpocetine and Gingko extract (which are not food supplements in UE), and substances naturally occurring in the human body: acetyl-L-carnitine, antioxidants (especially vitamin E) and precursors of phospholipid synthesis in cells, namely phosphatidylserine, phosphatidylcholine and citicoline. The authors concluded that pre-clinical (animal) data allow us to expect that some of the discussed substances may be effective, and results of some clinical trials also indicate positive effect. However, no definite conclusion can be reached.

For the last ten years little has changed in this respect. This is well illustrated by a recent article in a popular medical online bulletin of the Harvard University. A part of its title is: "Are any supplements helpful at all?" – and a part of its summary says: "There is no good evidence that dietary supplements help improve memory."

Citicoline as a Drug: Historical Outline

Citicoline is an international non-proprietary name (INN) of a substance whose chemical name is cytidinediphosphocholine (CDP-choline). In the 1950s, Eugene P. Kennedy and his

associates from Harvard University found that this substance is a natural precursor of biosynthesis of phospholipids that comprise cellular membranes [18]. It started to be used as a medicine in Japan at the beginning of the 1970s. First medical publications in English were on the use of CDP-choline in the treatment of Parkinson's disease [19] and – what may sound surprising today – acute pancreatic [20]. Soon after nootropic properties of CDP-choline were discovered, including stimulation glucose metabolism [21] and increasing concentrations of neurotransmitters noradrenaline, dopamine and serotonin [22]. These observations allowed citicoline to be registered in some European countries (e.g. in Italy, Spain and France) as a psychostimulant and nootropic (ATC N 06 B). It belongs to the subgroup of "other drugs", occupying position N 06 BX 06 next to the above-mentioned piracetam and vinpocetine.

A few years later an exciting perspective of using CDP-choline as a neuroprotective agent appeared. Lloyd A. Horrocks and associates from the Ohio State University in Columbus (USA) found that it inhibits breakdown of membrane phospholipids induced by cerebral ischaemia [23]. This invention was patented [24]. In Japan and in some European countries (e.g. Italy, Spain, France), and also in numerous countries in Asia and South America, citicoline for injection was registered as a prescription drug. The substance became quite popular especially in the 1980s, when a series of interesting studies were conducted and their results were published in 23 papers in the book 7A of volume 33 of a renowned international journal *Arzneimittel-Forschung* (currently *Drug Research*). Noticeably, studies in both animals and human volunteers or patients revealed minimal toxicity of the medicine. Also, pharmacokinetic studies showed that citicoline is fully metabolized to natural body components – which should not be surprising, since it is the natural constituent of cells. Results of clinical trials (mostly small) resulted in establishing the following indications for its use: Parkinson's disease, acute strokes and brain injuries, rehabilitation following strokes and brain injuries, lapses of memory and dementia [25]. However, in the other countries of the European Union and in the USA, citicoline has not become a registered drug.

A promising global career of citicoline as "the neuroprotective drug of confirmed efficacy" came to the end due to a series of multicentre, randomized, placebo-controlled and double-blind trials, results of which did not confirm its neuroprotective efficacy. The "black series" started with two American trials concerning strokes; the first one involved 349 patients and the second 899 patients [26, 27]. The last unsuccessful clinical trials include COBRIT conducted in the USA on 1,213 patients with brain injuries [28] and ICTUS conducted in Germany, Spain and Portugal involving 2,298 patients with ischemic strokes [29]. Reasons for the failure of these trials are uncertain, but critical analysis of pre-clinical experiments revealed that actually little is known about the mechanism of neuroprotective activity of this substance, and some interpretations which had been taken for granted are certainly not acceptable [30].

Citicoline as a Food

The above-mentioned unsuccessful clinical trials concerning ischemic stroke conducted at the end of 1990s in the USA used citicoline supplied by a Japanese pharmaceutical and biotechnological company Kyowa Hakko Kirin (abbreviated to: Kyowa). When it became clear that citicoline efficacy in strokes and brain injuries would not be confirmed, the company changed its attitude and decided to focus on low toxicity and low tolerance of this substance. At the end of May 2009, the branch of Kyowa in the USA announced [31], that based on proper legislation, it notified suitable authorities that a citicoline preparation, Cognizin, met the requirements of so called GRAS ("Generally Recognized as Safe") substance, i.e. is a substance safe enough to be added to food. Kyowa informed that it was going to offer citicoline on the American market as a component of foods and drinks. In August of the same year, a toxicological study on rats showing no adverse effects of citicoline doses up to 1 g/kg bw per day for the period of 90 days has been published [32].

At the end of March 2012, Kyowa submitted an application to the Food Safety Authority of Ireland (FSAI) for marketing authorization of citicoline as a food supplement being a source of cytidine and choline, which could be added to various food products and drinks. The maximum doses proposed in the application were 250 mg/serving in food products and 500 mg daily dose in dietary supplements. In June 2012, FSAI issued opinion that the application did not raise any doubts [33]. Although citicoline has to be treated as novel food in the European Union for procedural reasons, the substance itself and its components (cytidine, choline, phosphate) occur naturally in the body and are consumed in various food products, and their metabolic changes are well known. The same opinion was expressed by the EFSA panel on dietetic products, nutrition and allergies, which one year later, on behalf of the all European Union Member States, issued further positive opinion on the safety of citicoline as a new food [34]. On the basis of the above opinions and the positive outcome of voting that took place in EFSA on 1 July 2014, "Commission Implementing Decision authorizing the placing on the market of citicoline as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council" was taken and published in the Official Journal of the European Union. The annex to the decision includes analytical specification that must be achieved by citicoline (free base) as a new food approved for use in the European Union.

Effects of Citicoline on Memory

Two types of studies concerning effects of citicoline on human memory have been performed. The first included patients with memory disorders of various intensity (but excluding dementias). Most of these studies, in which citicoline was administered at different doses and with different routes of administration but for a short period of time (no longer than 3 months) to patients with subjective memory disorders, or mild or moderate vascular cognitive impairment, were conducted prior to 2005; their results are summarized in the meta-analysis [35]. Nine of these studies, in which the total number of 491 patients received citicoline and 435 placebo, assessed the effect of treatment on memory with the use of various methods, revealed statistically significant positive effect of the treatment. Positive effects of citicoline administration starting 7 weeks after brain stroke were also observed in a recent study involving 437 patients [36].

The second type includes a few studies performed with healthy volunteers. Although the number of participants was small, the outcomes are interesting and clearly positive. Two publications described metabolic effects of citicoline revealed by phosphorus magnetic resonance spectroscopy (^{31}P-MRS). This method enables noninvasive assessment on a selected area (voxel) of several cellular metabolites containing phosphorus, namely phosphomonoesters and phosphodiesters (phospholipid metabolites), inorganic phosphate, phosphocreatine and nucleoside triphosphates (mainly ATP). In the first study [37] 17 volunteers aged about 70 received 500 mg of citicoline daily in capsules for 6 or 12 weeks. Comparison of results obtained prior to and following supplementation revealed increase in phosphodiesters in the voxel located in *corpus callosum* by 7.6% on average. Moreover, the authors observed a positive correlation between the change in results of California Verbal Learning Test (a popular neuropsychological test used to assess verbal memory) and the change in the level of brain phosphodiesters. In the second study [38] ^{31}P-MRS was used to show effects of citicoline on the level of metabolites containing phosphorus in the frontal cortex and the occipito-parietal cortex. The study group contained 16 healthy subjects of middle age (47.3±5.4 years), who received citicoline at the dose of 500 mg or 2 g daily for 6 weeks. In the frontal lobes, there was increase in the phosphocreatine level by 7%, nucleoside triphosphates by 14% and the phosphocreatine/inorganic phosphate ratio by 32%. There were also changes in the level of phospholipid metabolites. Importantly, no changes were observed in the occipito-parietal lobes. In the interpretation of these results the authors pointed out that metabolic effect of citicoline occurred in the region of the cerebral cortex responsible for cognitive functions such as attention and memory. Citicoline supplementation may, therefore, reduce age-related cognitive and memory disorders by increasing energetic reserves and metabolites necessary to synthesize and maintain cell membranes in cortical areas of key importance to memory function.

Three other publications described the effect of citicoline (taken alone or in combination with caffeine) on cognitive functions in healthy subjects. A randomized, double-blind, placebo-controlled study including 60 women aged 40–60 years [39] using a *Continuous Performance Test* (CPT) revealed positive effects of citicoline received at the dose of 250 or 500 mg daily for 4 weeks. CPT is a neuropsychological test assessing the ability to react to significant stimuli and ignore insignificant stimuli. It is also used to assess attention. Attention is obviously quite closely related to working memory [40]. Two other randomized, placebo-controlled studies referred to short-term effects of citicoline in subjects aged 20–40 years. EEG revealed increased electric activity of the brain after receiving a drink containing 250 mg of citicoline, alone[41] or combined with caffeine [42]. The other study using neuropsychological tests revealed a significant improvement in attention and working memory after taking citicoline with caffeine.

Conclusions

Since the first use of citicoline in medicine at the beginning of the 1970s, the views on its safety and efficacy have undergone vast changes. In countries where it was registered as a drug, for many years it was administered only as injections and used only in hospital treatment or sold by prescription. Later it was also administered orally – and since it is surprisingly nontoxic and causes no adverse events, it became a para-pharmaceutical product in many countries. Finally, it received GRAS status in the USA and became a novel food in the European Community. This created a new situation of unrestricted legal distribution of citicoline, not only in the form of food supplements but also in various drinks and food products.

In agreement with definition of a food supplement, citicoline intake should benefit health thanks to its nutritional or physiologic effects. The scientific data discussed above allow identification of three target groups that may particularly benefit from citicoline supplementation. The first includes subjects with mild-to-moderate age-related memory disorders; the second – convalescents after brain strokes and injuries, and the third – healthy subjects of any age facing requirements of enhanced memory capabilities (for example preparing for exams), or increased concentration of attention (for example during night duties at work or long car drive). Other clinical data indicate that citicoline may retard progression of open angle glaucoma [43], and may be useful in treatment of addictions [44]. These issues, however, are beyond the scope of the present opinion.

Statement regarding conflict of interest

There is no conflict of interest at the date of the manuscript submission.

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