Differential effect of CDP-choline on brain cytosolic choline levels in younger and older subjects as measured by proton magnetic resonance spectroscopy

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Abstract

Phosphatidylcholine (PtdCho), which is essential for membrane integrity and repair, is reduced in brain cell membranes with age. Evidence from both animal and in vitro studies indicates that cytidine 5′ diphosphate choline (CDP-choline) can increase the synthesis of PtdCho; however, the effect of CDP-choline on brain choline metabolism has not previously been studied in human subjects. In this study, in vivo proton magnetic resonance spectroscopy (^{1}H-MRS) was used to measure brain levels of cytosolic, choline-containing compounds before and after single oral doses of CDP-choline. Three hours after dosing, plasma choline increased similarly in younger (mean age 25 years) and older subjects (mean age 59 years). However, while the choline resonance in brain increased by 18% on average in younger subjects, it decreased by almost 6% in older subjects (P=0/028). These results may be explained by a previously observed decrease in brain choline uptake, but not cytidine uptake, in older subjects. Additional intracellular cytidine following the administration of CDP-choline should lead to the increased incorporation of choline already present in brain into membrane PtdCho, which is not MRS-visible, consequently lowering the brain choline resonance below that of pre-treatment values. These results suggest that the cytidine moiety of CDP-choline stimulates phosphatidylcholine synthesis in human brain cell membranes in older subjects.

Introduction

Declines in cognitive function and neuronal plasticity with age have been associated with specific changes occurring in the central nervous system, including decreases in the functioning of cholinergic neurons in the brain[1, 2] and alterations in cell membrane composition, notably a reduction of choline-containing phospholipids[3, 5]. Moreover, acceleration of these age-related changes may be associated with the development of neurodegenerative disorders, including dementia.

These degenerative changes may be due, at least in part, by age-related alterations in the transport or metabolism of choline in brain. Although choline is a precursor of both the neurotransmitter actylcholine (ACh), as well as the phospholipids phosphatidylcholine (PtdCho) and sphingomyelin, essential structural components of cell membranes, very little choline is synthesized in brain[6, 8]. While choline can be synthesized by the liver[9], brain choline is largely obtained through dietary intake[10, 11], and transported across the blood-brain barrier by facilitated diffusion[12, 15]. An animal study[16], and more recently, human studies[17, 18] have shown that choline uptake into brain is reduced in older subjects. This reduction in choline uptake may contribute to the decrease in membrane PtdCho levels[3, 5] and cholinergic function observed in the brain with age[1, 2].

CDP-choline has been used clinically to treat patients with head trauma, cerebral vascular disease and various cognitive disorders[19]. The clinical efficacy of CDP-choline is presumably due to its ability to increase PtdCho synthesis in injured brain[20]. It may have a similar effect in aging brain, as CDP-choline has been reported to increase PtdCho in membrane preparations from 12-month-old mice[21].

In this study, in vivo ^{1}H-MRS was used to measure choline-containing compounds in human brain to determine whether single oral doses of CDP-choline would alter brain choline metabolism in younger and older adults.

Methods

Subjects were screened by medical history, physical examination and laboratory tests to be free of serious medical, neurological, or psychiatric illness. Following screening, subjects participated on 3 study days, each separated by at least 1 week. Before each study, subjects were asked to fast overnight, drinking only water. A baseline scan including proton spectroscopy was performed. Following the scan, one tube (5ml) of blood was drawn and immediately centrifuged for 10 min to separate plasma, which was then frozen on dry ice and stored in a -70°C freezer until assayed for choline and PtdCho. Subjects were given 0.5 g, 2.0 g and 4.0 g CDP-choline in a random order over the 3 study days, administered in a double blind manner. After a 3-h period, MR spectroscopy and blood drawing were repeated as before. The 3-h time point was chosen from the results of animal experiments which indicated that the choline moiety of exogenously administered CDP-choline is already being utilized in brain phospholipid biosynthesis at this point after dosing[22].

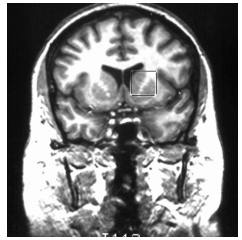


Fig.1 Transport and Metabolism of CDP-Choline

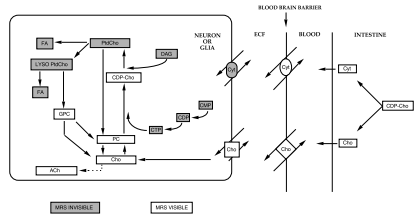


Fig.2 Change in Plasma Choline (nmol/ml) Three Hours After Ingestion of CDP-Choline

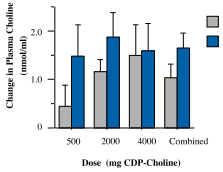
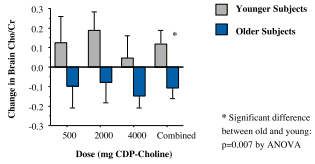


Fig.3 Change In Brain Cho/Cr Three Hours After Ingestion of CDP-Choline



Results

Plasma choline tended to be higher both before and after dosing in the older subjects relative to the younger subjects, and in some trials, this group difference reached statistical significance. When data from all trials are combined for each age group, plasma choline was found to be significantly higher in the older than in the younger subjects both at baseline (P=0.002), and post-treatment (P<0.0001). Changes in plasma choline due to CDP-choline administration (post-treatment minus baseline) are shown in Fig. 2. Plasma choline increased in each case after CDP-choline treatment. However, because of relatively large individual differences, the only statistically significant difference within each age group between baseline and post-treatment values is at the 2000 mg dose in the older subjects (P=0.002). The magnitude of these increases was not statistically different between old and young at any dose or when all doses were combined (P=0.11, repeated measures ANOVA). Within each age group, there was no statistically significant difference between doses in the magnitude of the increase in plasma choline (P=0.72, old; P=0.43, young). Also, there was no significant correlation between dose and increase in plasma choline, even though there appeared to be a trend for plasma choline to increase with CDP-choline dose in the young subjects (r=0.37; P=0.13).

As with plasma choline levels, plasma PtdCho was higher in older subjects both at baseline and post-treatment and, in most cases, this difference was statistically significant. These changes (post-treatment minus baseline) in plasma PtdCho were small and there were no statistically significant differences between baseline and post-treatment values within either group at any dose, or between old and young at any dose or for all doses combined (P=0.44, repeated measures ANOVA).

Brain Cho/Cr tended to be higher before treatment, but lower after treatment, in the older compared to the younger subjects. Because of large interindividual variance, the only statistically significant difference between baseline and post-treatment values was at the 4000 mg dose in the older subjects (P=0.03). Changes in brain Cho/Cr ratio due to CDP-choline administration (post-treatment minus baseline) are shown in Fig. 3.

Conclusions

This study is the first to show evidence that CDP-choline can increase PtdCho synthesis in vivo in human brain. Because the effects observed in this study may be due to the cytidine moiety of CDP-choline, studies on cytidine treatment alone would be valuable to define further its role in stimulating brain PtdCho synthesis in human subjects. The results of such studies should be interpreted with the knowledge that choline is used by cholinergic neurons both for PtdCho and Ach synthesis[23]. Therefore, administration of cytidine without concurrent administration of choline may channel available choline towards PtdCho synthesis and away from ACh synthesis.

Poster sponsored by Kyowa Hakko

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