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Research article

Effects of acute CDP-choline treatment on resting state brain oscillations in healthy volunteers

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HIGHLIGHTS

- CDP-choline affects human brain oscillations.
- Oscillatory changes mimic nicotinic stimulation.
- These observations allow extensions to clinical populations.

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ABSTRACT

CDP-choline (cytidine-5′-diphosphocholine) is a phospholipid used to treat cognitive disorders, presumably repairing and maintaining brain cell membranes. Additional mechanisms may include enhanced cholinergic neurotransmission as the α7 nicotinic receptor actions of choline and increased acetylcholine synthesis accompanying CDP-choline administration may modulate brain oscillations underlying cognitive processes. This study utilizes electroencephalographic (EEG) recordings in healthy volunteers to evaluate CDP-choline induction of an oscillatory response profile associated with nicotinic stimulation. Resting state EEG was acquired in 24 male volunteers administered low (500 mg) and moderate (1000 mg) doses of CDP-choline in a randomized placebo-controlled, crossover trial. Consistent with nicotinic agonist treatment, spectral analysis showed dose-dependent reductions in delta and increases in alpha oscillations, which were also accompanied by decreases in beta and gamma oscillatory activity. These findings support the posit that CDP-choline cognitive enhancement involves multiple mechanisms including facilitated nicotinic cholinergic action.

1. Introduction

CDP-choline, or citicoline is endogenous, an essential intermediate in the biosynthesis of structural phospholipids, chiefly phosphatidylcholine (PtdCho), in brain cell membranes [1]. CDP-choline treatment has shown clinical efficacy for cognitive disorders associated with cerebral vascular disease, head trauma, degenerative diseases (e.g., Alzheimer's disease) and normal aging [2]. Although its suggested pharmacological action has been the restoration of phospholipid biosynthesis, with PtdCho helping to restore and preserve the structure/function integrity of neuronal membranes in the damaged brain [3], its action appears to involve mechanisms beyond phospholipid metabolism.

CDP-choline is a form of the essential nutrient choline, a precursor of PtdCho as well as a donor in the metabolic pathways for biosynthesis of the neurotransmitter acetylcholine (ACh). Both ACh and its precursor, choline, are full agonists at nicotinic acetylcholine receptors (nAChRs), which play a critical role in normal cognition and are promising targets for novel treatments of cognitive dysfunction [4,5]. Oral administration of single doses of CDP-choline [6] and choline [7] increase plasma choline levels, as well as extracellular free choline in the brain as measured by magnetic resonance spectroscopy, but the presumed major quantitative fate of brain choline – rapid intracellular uptake and metabolic conversion to choline-bound phospholipids, not to ACh, may attenuate the marked cholinergic-related functional changes that would otherwise occur with the free ACh [8].

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Putative cholinergic actions associated with CDP-choline may be investigated noninvasively with quantitative electroencephalography (EEG), a neuroimaging tool [9] frequently used during the preclinical and clinical stages of drug discovery [10]. Distinct pharmaco-EEG profiles are associated with the pharmacodynamic actions of different classes of drugs [11,12] including nicotinic agonists such as nicotine, which in smokers induces a stimulant-like [13] electrocerebral activation pattern in spectral EEGs – accelerating the dominant oscillatory frequency, and increasing power of high frequency oscillations (alpha, beta, gamma) while decreasing power in low frequency oscillations (delta, theta) [14,15].

This study aims to assess the pharmaco-EEG profile of single oral doses of CDP-choline to healthy non-smoking volunteers, specifically evaluating the consistency of spectral EEG changes with nAChR stimulation. Although CDP-choline's clinically recommended dose range is 500–4000 mg, the range here was 500 and 1000 mg as nAChR activation is most evident with relatively low agonist concentrations, while high concentrations promote nAChR desensitization [16,17].

2. Methods

2.1. Participants

The study involved 24 healthy, right-handed males with a mean age of 21.3 years (SE = 0.99) recruited via local advertisements. Participants were screened initially by telephone and then by personal interview which included a medical exam and a personal and family psychiatric history assessment using the SCID-NP (Structured Clinical Interview–Nonpatient version for DSM-IV [18]) and FIGS (Family Interview for Genetic Studies [19]), respectively. Acceptance required no current medical or neurological illnesses, no personal or family psychiatric history (including substance abuse/dependence) and no use of medications. All were required to be nonsmokers, smoking less than 100 cigarettes in their lifetime (none in the past year) and exhibiting an expired air carbon monoxide level ≤ 3 parts per million, consistent with a nonsmoker status [20]. Participants were on normal diets, and reported no nutrition-related medical problems. All signed an informed consent for the study, which was approved by the research ethics board of the Royal Ottawa Mental Health Care Group.

2.2. Design

Participants were assessed in three test sessions (placebo and two doses of CDP-choline) conducted within a randomized, double-blind, crossover design, with session order being counterbalanced and each session being separated by 8–12 days to allow for CDP-choline elimination.

2.3. Procedures

Morning test sessions were between 9:00 a.m. and 11:00 a.m. following overnight abstinence from drugs, vitamins, food, and caffeine. Testing was initiated 4 h after treatment initiation and ended with assessment of adverse events and vital signs.

2.4. Treatment

CDP-choline was administered orally in two active doses, 500 mg (2×250 mg capsules) and 1000 mg (4×250 mg capsules) using a "double dummy" approach in which 4 capsules were administered in each test session (e.g., 2 placebo capsules and 2×250 mg capsules comprised the 500 mg test dose condition), including the placebo (cellulose) session. Single doses of CDP-choline dose-dependently raise choline plasma levels (peaking at 3–5 h), with an elimination half-life extending up to 56 h [21].

2.5. EEG

Three minutes of eyes-closed, vigilance-controlled resting state EEG activity was acquired in reference to the nose electrode, with scalp electrodes positioned at 8 regions (F3, Fz, F4, Cz, P3, Pz, P4, Oz) according to the 10–10 system [22]. An electrode at the mid-forehead site served as ground, and electrodes on orbital ridges and external canthi were used to monitor vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. Electrode impedances were kept below 5 kΩ and amplified signals (0.1–40.0 Hz amplifier bandpass filter) were digitized at 256 Hz. A minimum of 45 artifact-free 2-s duration EEG epochs were subjected to a Fast Fourier Transform algorithm (with a high-pass autoregressive filter, weighted by a 5% cosine taper) for computation of average absolute power (μV^2) in eight frequency bands as used previously [23] and include: delta (0.5–5 Hz); theta (6–8 Hz); $alpha_1$ (8.5–10 Hz); $alpha_2$ (10.5–12 Hz); alpha total (8.5–12 Hz); $beta_1$ (12.5–18 Hz); $beta_2$ (18.5–20.5 Hz) and $beta_3$ (21–30 Hz) frequency bands at each scalp region. Spontaneous gamma oscillations (30–60 Hz) in humans have not been systematically examined with respect to nicotine but were included here as an exploratory focus, with emphasis on absolute power.

2.6. Analysis

The Statistical Package for Social Sciences (SPSS, Chicago, IL) software was used to analyze log transformed absolute and relative (%) power value changes induced by CDP-choline treatment at the 8 scalp regions. Relative power values were derived by expressing power in each band as a percent of total power across all bands. Analysis of each absolute and relative band power index involved a separate repeated measures analysis of variance (ANOVA) with treatment (3 levels) and region (8 levels) as within-subject factors. Greenhouse–Geisser corrections were applied to all significant ($p < 0.05$) main and interaction effects, and Bonferroni-adjusted corrections were used in follow-up comparisons. To reduce the number of type I statistical errors, region affects were not followed up unless they interacted with treatment.

3. Results

There were no significant serious adverse events associated with CDP-choline (vs. placebo) and no adverse events led to discontinuation from the study. Heart rate and blood pressure vital signs were not affected by CDP-choline treatment.

Absolute power in the delta band was significantly affected by treatment ($F = 3.64$, df = 2/42, $p < 0.041$) and region ($F = 28.83$, df = 7/147, $p < 0.0001$). Compared to placebo, power was reduced ($p < 0.03$) with both doses of CDP-choline but reached significance only with the 1000 mg dose (Fig. 1). No significant treatment-induced changes were observed for absolute power in theta and alpha bands but significant treatment *x* region interactions were shown with power in $beta_2$ ($F = 2.39$, df = 14/294, $p < 0.05$) and $beta_3$ bands ($F = 2.55$, df = 14/294, $p < 0.04$). For $beta_2$, power at F3 was reduced by the 1000 mg dose compared to both placebo ($p < 0.05$) and the 500 mg doses ($p < 0.02$), and similar reductions with 1000 mg were shown at F4 when compared to the placebo ($p < 0.04$) and 500 mg CDP-choline ($p < 0.04$) doses (Fig. 2). Power reductions were also evidenced at C3 ($p < 0.04$) but with the 1000 mg dose reducing power only when compared to placebo (Fig. 1). $Beta_3$ power was also reduced at F3 ($p < 0.05$) and F4 ($p < 0.05$), as well as at C4 ($p < 0.03$) with the 1000 mg dose compared to placebo (Fig. 2). Follow-up comparisons of a significant