DOI 10.1007/s11055-022-01247-x
Neuroscience and Behavioral Physiology, Vol. 52, No. 3, March, 2022

Molecular and Clinical Aspects of the Action of Cytidine Diphosphocholine on Cognitive Functions

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Translated from Zhurnal Nevrologii i Psikhiatrii imeni S. S. Korsakova, Vol. 121, No. 5, Iss. 1, pp. 88–97, May, 2021. Original article submitted March 2, 2021. Accepted March 28, 2021.

Objectives. To systematize publications on drugs based on cytidine diphosphocholine (CDP-choline). **Materials and methods.** Systematic computer analysis of all currently available publications on CDP-choline (1750 publications in PubMed) using topological analysis theory for big data. **Results.** CDP-choline is required for acetylcholine biosynthesis, phospholipid metabolism, and DNA methylation. This article sequentially considers the effects of CDP-choline on acetylcholinergic and other types of neurotransmission and the anti-inflammatory and neuroprotective effects of CDP-choline, as well as the influences of this molecule on fat metabolism and gene expression in the context of the postgenomic paradigm (particularly elevated expression of nicotinic and muscarinic acetylcholine receptors). Results from basic and clinical studies of CDP-choline in the treatment of cognitive impairments associated with cerebral ischemia and neurodegeneration are presented. **Conclusions.** The pharmacological effects of CDP-choline are realized via multiple molecular mechanisms contributing to the nootropic actions of this molecule.

Keywords: cognitive disorders, molecular pharmacology, citicoline, Neipilept.

Choline and its derivatives phosphatidylcholine, cytidine-diphosphocholine (CDP-choline or the contracted synonym citicoline) are widely used in neurological practice. The biological effects of the compound choline have the greatest importance in the neuromuscular system, where choline derivatives are precursors of acetylcholine. Acetylcholine deficit is linked with decreased memory in ischemic and neurodegenerative diseases of the brain [1], degradation of phospholipid metabolism in the liver, and impairment of the DNA methylation required for regenerating neurons [2, 3].

In pharmacology, CDP-choline is conventionally regarded as an intermediate metabolite in phosphatidylcholine synthesis. Intravenously administered CDP-choline undergoes hydrolysis to form choline and cytidine. Choline is rapidly taken up for the synthesis of acetylcholine and phospholipids for neuron and mitochondrial membranes, while cytidine is included in cytidine nucleotides. However, in the concept of postgenomic medicine, this mechanism of action seems very simple and is unable to explain many of the pharmacological effects of CDP-choline (particularly the long-term influences on cognitive functions) [4].

Materials and Methods. This work presents the results of systematic analysis of all the available scientific literature on basic and clinical research into the effects of CDP-choline, one of the main choline derivatives used in neurology. Use of the search term "Cytidine-5-diphosphocholine OR CDP-choline OR citicoline" in the biomedical publications database PubMed revealed 1750 references. We undertook systematic computer analysis of this set of publications using contemporary analytical methods for big data developed in the framework of topological [5] and metrical [6] approaches to recognition tasks [7, 8].

Results. Systematic analysis of the literature identified 145 informative biomedical terms distinguishing publications on the neurology of CDP-choline from publications forming a control set. The control set of texts included 1800 articles ran-

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domly selected from nore than 5,500,000 articles found using the search term "clinical NOT citicoline NOT cytidine-5-diphosphocholine NOT CDP-choline." Annotation of these terms in relation to the corresponding molecular-biological processes, neurological symptomatology, and ICD-10 diagnoses identified the 89 most informative terms, which were found significantly more frequently in the set of publications on CDP-choline than in controls (3–84 times more frequently, $p < 0.05$, for each of the 89 terms). The result yielded a map of the molecular physiology of the neurological actions of CDP-choline (Neipilept), with two clusters of informative biomedical terms: "Inflammation" and "Acetylcholinergic neurotransmission."

Analysis of the "Inflammation" cluster showed that use of CDP-choline decreased the inflammatory response to interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α). CDP-choline-induced decreases in inflammation promote activation of neuron sprouting via activation of signals from neurotrophin TRKA and TRKC receptors and brain-derived neurotrophin factor (BDNF) receptors and the elimination of depression of synaptic function. The anti-inflammatory effects of CDP-choline are linked with activation of acetylcholinergic neurotransmission. By increasing nicotinic receptor activity, acetylcholine and CDP-choline regulate the expression and levels of choline-O-acetyltransferase and other elements of choline metabolism and decrease NF-ϰB activity, this compound being involved in producing the effects of proinflammatory cytokines. Adequate provision of zinc ions to body cells is also important for realization of these effects of choline formulations. In addition, activation of acetylcholinergic neurotransmission is also important for normalizing insulin-dependent glucose transporters, endorphinergic neurotransmission, and dopaminergic neurotransmission in the cerebral cortex. Maintenance of these processes helps inhibit neurodegenerative changes. CDP-choline also decreases inflammation via other molecular mechanisms (γ-interferon synthesis, toll-like receptor 1 signals, decreased IL-1a synthesis, regulation of B lymphocytes, etc.), promotes compensation of impaired liver function (cholestasis, steatohepatosis, obesity, fatty acid metabolism, regulation of triglyceride synthesis), affects neurotransmitter homeostasis: GABA, glycine, nerve growth factor (NGF), etc. We emphasize that phosphatidylcholine biosynthesis, the rational basis of the "membrane repair" hypothesis, is just one of dozens of processes regulated by CDP-choline [9].

Overall, analysis of the metric pattern identified a set of informative keywords describing important but rarely considered molecular mechanisms of CDP-choline action. On the basis of these keywords, further PubMed searches were run and these identified 65 representative publications describing the molecular mechanisms and clinical aspects of the actions of CDP-choline.

CDP-choline and acetylcholinergic neurotransmission. Citicoline treatment is known to have favorable influences on cognitive functions in vascular dementia [10]. These effects are associated primarily with the maintaining effects of CDP-choline on acetylcholinergic neurotransmission. The neuroprotective effect of citicoline is also associated with increases in brain acetylcholine levels and, as a result, decreases in the symptoms of cerebral ischemia [11].

The main effect of CDP-choline on acetylcholinergic neurotransmission is activation of nicotinic acetylcholine receptors. In particular, by activating central nicotinic receptors in rats, CDP-choline weakens scopolamine-stimulated suppression of the startle reflex induced by sudden loud noises. In experimental studies, scopolamine significantly decreased the levels of reflexes, while i.p. CDP-choline weakened the effects of scopolamine [12].

Simultaneous use of CDP-choline (500 mg/day) with the cholinesterase inhibitor galantamine (16 mg/day) promoted activation of α7-nicotinic acetylcholine receptors. Activation of α7-nicotinic receptors normalized the so-called encephalographic mismatch response in healthy volunteers. This effect of CDP-choline corresponded to improvements in speech perception [13], including improvements in the understanding of speech and other auditory stimuli [14]. CDP-choline maintains the sensitivity of α7 receptors in patients with schizophrenia and improves verbal memory [15]. Activating supraspinal α7-nicotinic acetylcholine receptors, CDP-choline promotes suppression of pain [16]. In experiments, CDP-choline stimulated cholinergic neurotransmission [17], including via regulation of muscarinic acetylcholine receptor levels in the brain [18].

Results from postgenomic chemotranscriptome studies indicate that CDP-choline can increase the expression of genes encoding proteins involved in choline metabolism (Table 1) and genes encoding nicotinic and muscarinic acetylcholine receptors, as well as genes involved in choline transport [4], which corresponds to realization of the clinically observed long-term nootropic action of Neipilept.

CDP-choline and the metabolism of other neurotransmitters. Cognitive functions are realized via a close interaction between different neurotransmitter systems in the brain. CDP-choline influences the activity of the GABAergic, opioidergic, adrenergic, and dopaminergic systems. Studies on a model of acute pain in rats demonstrated an anti-pain effect of CDP-choline in interaction with opioid and GABA receptors. Intracerebroventricular administration of CDP-choline suppressed pain reactions by activating supraspinal α7 nicotinic acetylcholine receptors. At the same time, the opioid receptor antagonist naloxone and the $GABA_B$ receptor antagonist CGP-35348 inhibited the antinociceptive effect of CDP-choline in experimental studies [16].

CDP-choline countered the effects of cerebral hypoxia in rats induced by impairment of the synthesis of the neurotransmitters dopamine and noradrenaline in the hypothalamus and corpus striatum in the brain. Hypoxia decreased the 3-methoxy-4-hydroxyphenylacetic acid level and the dihydroxyphenylacetic acid level in the corpus striatum of the brain and the noradrenaline concentration in the hypo-

TABLE 1. Proteins Mediating the Physiological Effects of Choline Substances. The "Expr." Column Shows the Results of Chemotranscriptome Studies of the Effects of CDP-Choline on Neuron Precursor Cells [4]

Protein	Function	Gene	N	Expr.
Choline metabolism				
Choline dehydrogenase	Betaine synthesis	*CHDH*	1	0%
Choline kinase	Phosphatidylcholine synthesis	*CHK*	1	–7%
Choline O-acetyltransferase	Acetylcholine synthesis	*CHAT*	1	+23%
Choline phosphatidyltransferase	Phosphatidylcholine synthesis	*PCYT1A PCYT1B*	2	+25%
Butyrylcholinesterase	Acetylcholine synthesis and degradation	*BCHE*	1	0%
Acetylcholinesterase	Acetylcholine hydrolysis	*ACHE*	1	–8%
Choline phosphotransferase	Phosphatidylcholine synthesis	*CHPT1*	1	0%
Choline ethanolamine phosphotransferase	Phosphatidylcholine synthesis	*CEPT1*	1	+11%
Lecithin retinol acyltransferase	Retinyl ester synthesis from transretinols involving phosphatidylcholine	*LRAT*	1	+8%
Lecithin cholesterol acyltransferase	Synthesis of cholesterol esters and cholesterol transport from peripheral tissues to the liver	*LCAT*	1	0%
Choline transport				
CDW92 protein	Intracellular choline transport	*CDW92*	1	0%
Phosphatidylcholine-binding protein	Transfer of choline derivatives between intracellular organelles	*PCTP*	1	–12%
Choline transporter 22/1	Specific choline transport	*SLC22A1*	1	+11%
Choline transporter 44/1	Specific choline transport	*SLC44A1*	1	+10%
Choline transporter 5/7	Specific choline transport	*SLC5A7*	1	+8%
Choline transporter 18/3	Acetylcholine transfer within secretory synaptic vesicles	*SLC18A3*	1	+6%
Cholinergic signal transmission				
Nicotinic receptors	Nicotinic acetylcholine receptors types A2, A3, A4, A5, A6, A7, A9, A10, B2, B3, and B4	*CHRNA1* etc.	11	+12%
Muscarinic receptors	Receptor mediating the effects of acetylcholine via G-proteins: types M1, M2, M3, M4, and M5	*CHRM1* etc.	5	+10%
Ca-dependent phospholipase A2	Phosphatidylcholine hydrolysis on intracellular signal transmission, types GIID, GIIe, GIIF, GIII, GV, GX, GXII, GXIII, D1, and D2	*PLA2G5* etc.	10	+14%
Thrombocyte-activated acetylhydrolase	Inactivates platelet activating factor and the corresponding phospholipids	*PLA2G7*	1	+9%
Cell cycle kinase 2/5	Regulation of the cell division cycle, possibly choline-dependent	*CDC2L5*	1	0%

N is the number of corresponding genes; Expr. is the dose-dependent effect of CDP-choline (% change for every additional μM).

thalamus. CDP-choline (1000 mg/kg/day p.o. for 1–3 days) inhibited impairments to noradrenaline and dopamine metabolism [19].

The effects of CDP-choline have been best studied in relation to dopamine. Activation of dopaminergic transmission is required for attention-switching processes in humans, so impairments to dopamine metabolism are associated with impaired concentration, including attention deficit hyperactivity disorder [20]. CDP-choline modulates dopamine release in the corpus striatum [21] and decreases loss of dopaminergic neurons induced by glutamate in primary mesencephalic cell cultures [22]. Even at quite small doses (50 mg/kg), CDP-choline increased the rate of dopamine and tyrosine biosynthesis in the corpus striatum in rats [23].

Experimental studies have established the influence of CDP-choline on changes in dopamine and acetylcholine receptor levels in the corpus striatum in aged mice, including increasing the density of dopamine receptors by 11% (at a CDP-choline dose of 100 mg/kg) and 18% (at a dose of 500 mg/kg). The density of muscarinic acetylcholine receptors was increased by 6% (at a dose of 100 mg/kg) and 17% (at a dose of 500 mg/kg) [18].

Extreme dopaminergic insufficiency is a characteristic of Parkinson's disease (PD), which is associated not only with impaired motor functions, but also decreased cognitive functions. Studies in a model of Parkinson's disease induced by 6-hydroxydopamine (6-HD) in rats confirmed the neuroprotective effect of citicoline, with decreases in the cytotoxic effect of 6-HD on SH-SY5Y neurons and decreases in the loss of dopaminergic neurons in the substantia nigra [3]. There is experience of the use of CDP-choline in combination with levodopa in the treatment of PD [20].

The anti-inflammatory effects of CDP-choline. Decreases in excessive inflammatory reactions in the CNS are an obligatory condition for the maintenance of cognitive functions. Chemoreactive analysis of CDP-choline pointed to complex anti-inflammatory actions [24]. In experiments, CDP-choline preserved mitochondrial function and produced decreases in oxidative stress and the levels of alanine aspartate aminotransferase (AST), alanine aminotransferase (ALT), and TNF-α, with parallel increases in the blood concentration of the lipid mediator resolvin D1 [25]. We recall that resolvin D1 is one of the most important derivatives of ω-3-polyunsaturated fatty acids and is involved in the physiological resolution of inflammation [26].

In experimental studies in rats, CDP-choline (125 mg/kg/day) prevented mitochondrial damage and impaired renal function induced by mercury poisoning (mercury is also a neurotoxin). Citicoline decreased the synthesis of proinflammatory IL-1 and IL-6 and oxidative injury to mitochondrial DNA and increased creatinine and urea clearance from the blood [27].

In a rat model of stroke, use of CDP-choline (1000 mg per kg) 30 min and 24 and 48 h after induction of pathology was just as effective as thrombolysis by administration of recombinant tissue plasminogen activator. Both CDP-choline and plasminogen activator produced significant reductions in infarct volume on the background of decreased TNF-α and IL-6 concentrations [28].

Studies in models of neuropathic and inflammatory pain demonstrated the antinociceptive effect of CDP-choline [29], which involved α7-nicotinic receptors [30]. Thus, activation of α7-nicotinic receptors by CDP-choline was linked with anti-inflammatory, antinociceptive, and procognitive effects.

Neuroprotective effects of CDP-choline. In acute ischemic stroke, citicoline provided neuroprotection, weakening glutamate excitotoxicity, oxidative stress, and neuron apoptosis and decreasing dysfunction of the blood:brain barrier (BBB). Citicoline influences survival and neurological and behavioral outcomes in mice subjected to transient hyperglycemia and hypovolemic hypoxia [31]. In the subacute phase of ischemic stroke, citicoline enhances neurotransmitter metabolism, synaptogenesis, and angiogenesis [32]. Assessment of the neuroprotective, anticonvulsant, sedative, and anxiolytic activities of CDP-choline in rats demonstrated significant improvements in indicators in a maze test ($p < 0.05$) [33].

In stroke induced by permanent occlusion of the middle cerebral artery in rats, CDP-choline increased the expression of brain plasticity markers, decreased cerebral infarct volume on MRI scans, reduced the number of cells undergoing apoptosis, and increased BrdU uptake in the periinfarct zone (a marker of cell division), vascular endothelial growth factor (VEGF), and synaptophysin, stimulating functional recovery of the brain [34].

Use of CDP-choline improved the state of the BBB. For example, i.p. CDP-choline at a dose of 100 mg/kg decreased cerebral edema, while a dose of 400 mg/kg significantly reduced BBB impairments in a model of traumatic brain injury in rats [35]. In addition, administration of citicoline decreased acute hypoglycemia-induced neuron death and loss of immunoglobulins through the damaged BBB, also increasing choline acetyltransferase expression, this enzyme being involved in phosphatidylcholine biosynthesis [36].

The neuroprotective effects of CDP-choline are mediated by a variety of molecular mechanisms, including: 1) improvements in brain energy metabolism (increases in phosphocreatine and ATP in the frontal lobe of the brain, as indicated by MRI data) [37], including mechanisms involving magnesium ions [38]; 2) decreased neuron apoptosis (decreased expression of procaspase-3, activated caspase-3, and fragmented nuclear DNA) [39, 40]. More specific molecular effects have also been recorded for CDP-choline in cerebral ischemia: decreased phospholipase PLA2 activity [41], inhibition of ERK1/2 and MEK1/2 signal pathways [42], and regulation of IRS1 [43] and sirtuin-1 [44] proteins.

For example, studies in a model of transient cerebral ischemia in gerbils showed that citicoline decreased phospholipase A2 activity (an enzyme partially degrading neuron membranes) and inhibited the formation of hydroxyl radicals. PLA2 activity increased significantly ($p < 0.05$) in both the membrane and mitochondrial fractions after cerebral ischemia and this response was significantly weakened by citicoline ($p < 0.01$), though citicoline had no effect on PLA2 enzyme activity in vitro [41].

Studies in a model of transient occlusion of the middle cerebral artery in rats showed that citicoline induced angiogenesis and improved survival of vascular endothelial cells in the brain on the background of elevated expression of the protein insulin receptor substrate IRS1. Inhibition of the expression of the *IRS1* gene suppressed the neuroprotective and angiogenic effects of citicoline [43].

The neuroprotective effects of CDP-choline in experimental stroke are accompanied by increases in the expression of sirtuin-1 protein (the *SIRT1* gene) in the brain. Resveratrol (an activator of sirtuin-1 protein) increased the neuroprotective effect of CDP-choline, while inactivation of the *SIRT1* gene led to weakening of the effect of CDP-choline [44]. We recall that sirtuin-1 is an NAD-dependent deacetylase regulating the epigenetic code of the genome, inflammation (inhibition of NF-ϰB), and the effects of insulin (deacetylation of peroxisome proliferator γ receptor coactivator protein) [45].

TABLE 2. Genes and Proteins Whose Expression Increases in Response to CDP-Choline. "% Chemo" Shows Percentage Changes in Expression per 1 μM of Substance (chemotranscriptome analysis of CDP-choline in NPC.TAK neurons) and Experimental Confirmation

Gene	Protein	Main functions	% Chemo	Expt.
CHAT	Choline acetyltransferase	Acetylcholine biosynthesis	22.3	[36]
SIRT1	Sirtuin-1	Neuroprotection, including in hyperinsulinemia	9.4	[44]
IRS4	Insulin receptor substrate protein	Increased sensitivity of neurons to insulin	7.2	[43]
VEGFC	Vascular endothelial growth factor	Brain vascularization	12.2	[34]
SYP	Synaptophysin	Transport of neurotransmitter into synapses	8.3	[34]
OPRD/M/K	Opioid receptors types δ, μ, and ϰ	Anti-inflammatory and analgesic effects	17–29	[16]
GABRB1/3	$GABA_B$ receptors types 1 and 3	Analgesic effects	5.8–9.4	[16]
DRD2/3/4	Dopamine receptors types 2, 3, and 4	Maintenance of attention, assessment of negative experience	10–50	[18]
CHRM4/5	Muscarinic receptors types 4 and 5	Long-term effects of acetylcholine in the CNS	8.4–12.9	[18]

Thus, the neuroprotective effect of CDP-choline is accompanied by anti-inflammatory and antihyperinsulinemic actions, reductions in BBB dysfunction, and increases in neuron energy supply. Timely use of CDP-choline is therefore useful in patients suffering from chronic cerebral ischemia on the background of diabetes mellitus, traumatic brain injury, and other diseases accompanied by impairments to BBB integrity (viral and bacterial infections, alcoholic and other toxic brain damage, etc.).

The neurotrophic effects of CDP-choline. The neuroprotective effects described above suggest increased neuron survival in stress conditions. The neurotrophic effects imply stimulation of neuroregenerative processes: dendrite sprouting, axon growth, formation of more highly branched neuron networks.

CDP-choline and its metabolites cytidine and choline have marked neurotrophic actions. Studies in a model of sciatic nerve injury in rats showed that use of CDP-choline led to a significantly greater increase in scores for recovery of limb movement activity (SFI) as compared with choline, cytidine, and placebo. Use of CDP-choline increased the number of neurons by 50% or more, while use of choline alone or cytidine alone did not produce any significant increase in the number of axons [46]. Citicoline stimulated neurite regeneration in the retina in rats just as much as neurotrophic factors BDNF and NT-4 (neurotrophin-4) [47]. Administration of CDP-choline to neonatal rats induced stable increases in the dendritic complexity of the neural neurons in the somatosensory cortex on the background of increases in neurite length, the number of branch points, and total cortical area [48].

In the clinic, citicoline improved the morphology and function of nerve endings in the ophthalmic branch of the trigeminal nerve in the cornea in patients with diabetes [49] and improved visual function in patients with glaucoma [50].

The previously noted results of chemotranscriptome analysis of the CDP-choline molecule [4] confirm the molecular mechanisms mediating the neuroprotective effects of CDP-choline described above. For example, chemotranscriptome analysis showed that CDP-choline increases the expression of most of the genes discussed in the present report: *SIRT1* (encodes sirtuin-1), *IRS1* (encodes insulin receptor substrate 1 protein), *VEGFC* (encodes vascular endothelial growth factor C), *CHRM4* (encodes muscarinic acetylcholine receptor-4), and others. Results from chemotranscriptome analysis have supported investigations of individual genes and the proteins corresponding to them (Table 2, Fig. 1).

CDP-choline counteracts hepatic encephalopathy. Fatty dystrophy of the liver arising as a result of poor diet, alcohol consumption, or genetic defects is associated with cognitive impairments. Hepatic encephalopathy may also be iatrogenic [51]. CDP-choline is unique in the sense that it produces an indirect nootropic action by normalizing lipid metabolism in the liver. In particular, CDP-choline prevents free saturated fatty acid release in cerebral ischemia [52], which promotes improvements in choline transport [53]. CDP-choline-activated diacylglycerol synthetase CdsA coordinates cell growth and fat accumulation involving phosphatidylinositol and signals from insulin receptors [54]. CDP-choline is therefore the substance of choice for the treatment of cognitive impairments on the background of fatty dystrophy of the liver.

Use of CDP-choline in the treatment of cognitive impairments in ischemia. The neuroprotective and neurotrophic effects of CDP-choline and the effects of CDP-choline on neurotransmission, lipid metabolism, and decreases in inflammation are mediated by the various actions of this molecule on cognitive functions. The complex nootropic action of CDP-choline has been demonstrated in experimental studies in various models of cerebral ischemia [55, 56] and has been supported by results from clinical investigations. For example, a study of patients with acute ischemic stroke found that CDP-choline (1000 mg/day, 15 days) led to decreased cognitive impairment on the mini mental state ex-

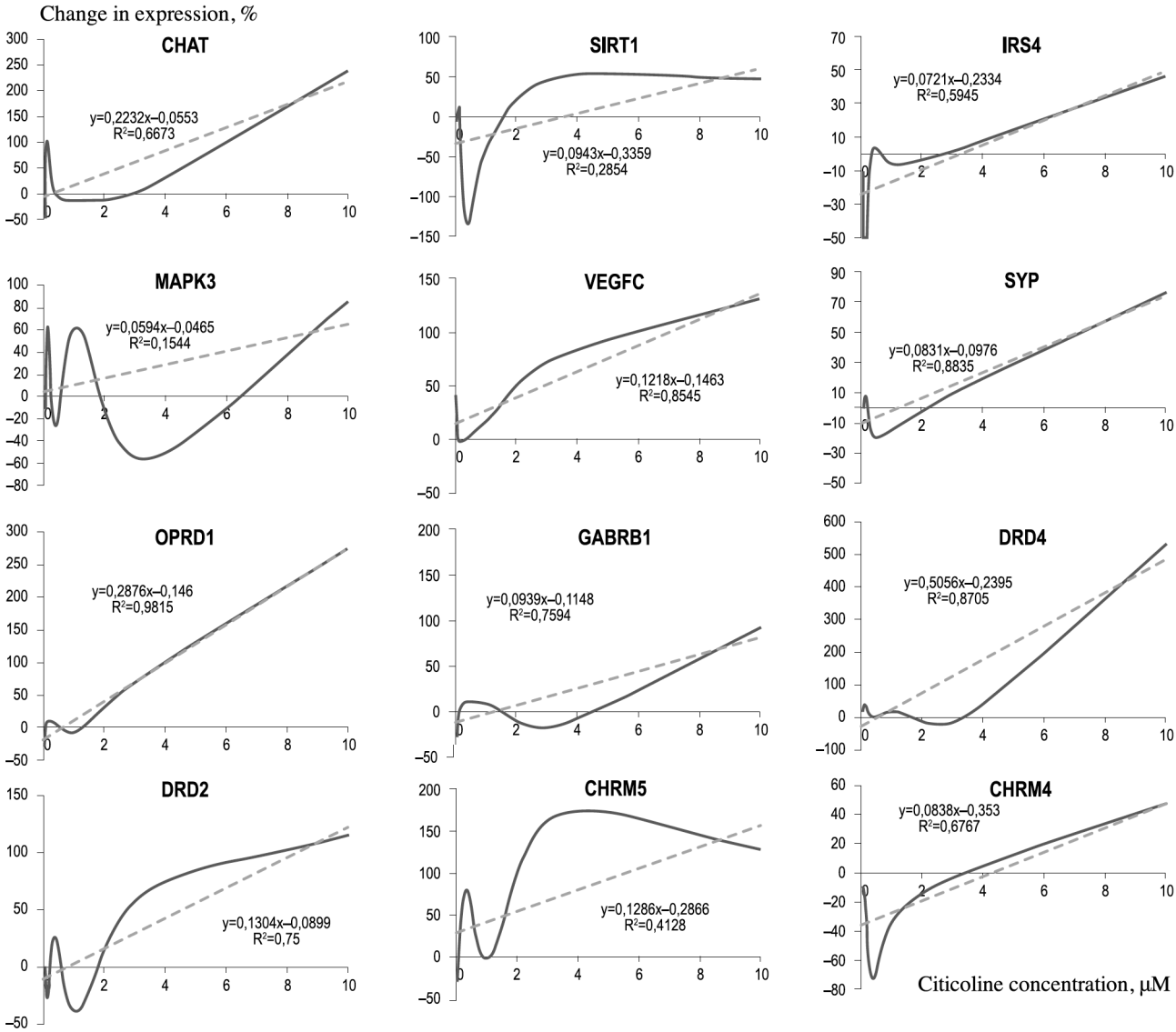

Fig. 1. Examples of the dose-dependent effects of citicoline (Neipilept) on the expression of genes realizing the neuroprotective and neurotrophic effects of the molecule (chemotranscriptome analysis of NPC.TAK neurons).

amination (MMSE), regression of neurological symptomatology on the NIHSS, and improved memory and motor activity (Rankin scale, Bartel scale, Rivermead Mobility Index) [57].

CDP-choline (500–4000 mg/day, p.o., 6–12 weeks) has been shown to be effective and safe when use is initiated 24–48 h after the development of acute ischemic stroke (n = 4191). Significant improvements in patients' status on the NIHSS and Bartel and modified Rankin ($p < 0.05$) scales were seen at six weeks. At 12 weeks of treatment, there were further improvements in study parameters which were significantly more marked on use of high doses (>2000 mg/day) [58].

Long-term treatment with CDP-choline prevented reductions in cognitive functions and predicted better quality of life after ischemic stroke [59]. Meta-analysis of 10 randomized trials of patients with acute ischemic stroke demonstrated an increased chance of faster recovery of independence in patients receiving CDP-choline (OR 1.56, 95% CI 1.12-2.16) [60].

CDP-choline displays nootropic effects in patients with chronic cerebral ischemia of different origins. A multicenter trial of citicoline (1000 mg/day, 30 days) in patients with arterial hypertension and/or atherosclerosis (n = 736, 64.5 ± 8.7 years old) showed significant restoration of cognitive functions on the MSSE, with correction of impaired visuospatial coordination on the CDT scale, and decreased severity of depression on the MGDS [61].

CDP-choline improved memory indicators in elderly patients with memory impairments but without dementia (n = 24; 66.12 ± 10.78 years old). On the background of use of CDP-choline, significant improvements were seen in

word memorization (5.17 ± 1.1 omissions in controls compared with 3.95 ± 1.2, $p < 0.005$), immediate object recall (6.5 ± 1.6 omissions in controls vs. 5.5 ± 1.2, $p < 0.05$), and delayed object recall (8.5 ± 2.1 omissions in controls vs. 6.7 ± 2.4, $p < 0.005$), along with decreases in systolic arterial blood pressure [62].

Asthenic, cognitive, and psychoemotional impairments are typical of cerebral ischemia. Apart from the nootropic action of CDP-choline in ischemia, we note that use of CDP-choline (500 mg/day, 30 days) could also reduce cognitive, emotional, autonomic, and asthenic disorders in healthy subjects without ischemia (students, university teachers, $n = 58$, age 27.8 ± 12.1 years) [63].

Basic and clinical studies of CDP-choline in neurodegenerative pathology. Neurodegenerative pathology is generally accompanied by cognitive impairments, especially in elderly and old people. A double-blind, placebo-controlled study of CDP-choline (1000 mg/day, 12 weeks) in mild and moderate Alzheimer's disease demonstrated improvements in brain bioelectrical indicators, cerebral blood flow, and cognitive capacities in the patients. Citicoline improved cognitive functions in patients with the E4 genetic variant of apolipoprotein E (APOE4), which corresponds to an elevated risk of atherosclerosis and dementia (decreases in ADAS scores from placebo: –3.2 ± 1.8 points, $p < 0.05$). Transcranial dopplerography data indicate that use of CDP-choline led to increases in cerebral blood flow rate as compared with placebo ($p < 0.05$). Patients given citicoline showed improvements in brain bioelectrical activity in the form of increases in the percentage α and θ activity and decreases in δ activity, particularly marked in the left temporal lobe. CDP-choline treatment also produced significant reductions in blood IL-1β levels [64].

Analysis of two retrospective cohort studies in elderly patients with Alzheimer's disease ($n = 563$) showed that treatment with CDP-choline and acetylcholinesterase inhibitors for three months led to significant improvements on the MMSE (+2–3 points compared with the control group given acetylcholinesterase inhibitors only). Treatment improved cognitive functions and mood. The frequency of side effects (irritability, nausea, headache) was not significantly different from that in controls [65].

The nootropic properties of CDP-choline, which result from the set of molecular mechanisms described above, can be enhanced by the antihypoxant/antioxidant ethylmethylhydroxypyridine succinate (EMHPS). CDP-choline and EMHPS act synergistically in elderly patients with chronic cerebral ischemia ($n = 40$, age 54–72 years) [66]. The detailed description of the mechanisms of the molecular synergy between CDP-choline and EMHPS is very complex, as these molecules also act on the transcription of numerous genes and on the activity of proteins in the proteome [4].

Chemoreactome analysis of the synergism between EMHPS and a number of nootropic substances showed that CDP-choline can increase the pharmacological properties of EMHPS in three directions: 1) neuroprotective activity and modulation of neurotransmission (inhibition of amyloid synthesis, activation of serotonin and cannabinoid receptors), 2) anti-inflammatory activity (blockade of the effects of proinflammatory factors TNF-α, IL-1, IL-6, and leukotriene B4), and 3) antithrombotic activity (inhibition of platelet aggregation by inhibition of the effects of thromboxane A2) [24].

Conclusions. In some cases, maintenance of the brain's mnestic and cognitive functions requires use of nootropic drugs which improve the neurobiochemistry of the brain. CDP-choline occupies a special place amongst the nootropes, simultaneously being an acetylcholine precursor and a central component of phospholipid metabolism which detoxifies homocysteine via the betaine pathway and DNA methylation. In addition, CDP-choline also has complex influences on the activity of the GABAergic, opioidergic, adrenergic, and dopaminergic neurotransmitter systems; it has anti-inflammatory, neuroprotective, and neurotrophic properties. CDP-choline promotes increases in the expression of nicotinic and muscarinic acetylcholine receptors, which is important in producing its long-term effects. Results from basic and clinical research have confirmed the importance of CDP-choline in the treatment of cognitive impairment in ischemic and neurodegenerative diseases of the CNS.

This work was carried out in the framework of state task "Adaptive morphofunctional rearrangements of organs and systems on physical loading as a model of rehabilitation measures after formation of total cerebral hypoxia in rats depending on the state of higher nervous activity" (2018–2020), part 2, "Applied Scientific Research." Study details: unique registration No. 730000F.99.1.BV10AA00006. Analysis of data on demyelination was funded by the a grant from the Russian Foundation for Basic Research (Project No. 20-12-00175).

The authors declare no conflict of interest.

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