# Drug Synergism as the Basis of Rational Neuroprotection

**M. V. Putilina and N. V. Teplova**

Optimization of the choice of neuroprotective therapy regimens in patients with cerebrovascular diseases (CVD), taking into account the synergism of drug interactions, is a basic approach in clinical practice. Unfortunately, modern pharmacology has no unified way of establishing synergistic spectra of drug actions, which would allow systematic investigation of the effects of combinations of drugs. An approach based on studying detailed mechanisms of action suggested combinations of drugs with the greatest possible synergism (by summation and potentiation of effects) for various directions in the treatment of neurological diseases. Examples of rational neuroprotection are considered, using Cortexin, citicoline, and antioxidants.

The beginning of the 21st century was marked by the global COVID-19 pandemic and the problems associated with its consequences. The post-covid period has relatively arbitrary time characteristics and involves a variety of neurological manifestations [1]. At the same time, the burden of cerebrovascular disease (CVD) has not diminished. In 2019, a significant increase (by 36%) in the frequency of CVD among the population aged 35–64 years was recorded around the world, of which 19% were primary and 48% were recurrent cases [2, 3]. The age composition of the planet is changing: the number of elderly people in 2050 will reach 2 billion [4, 5]. This population sector has larger numbers of comorbid conditions, decreased potential for adaptation to both exogenous and endogenous influences, and a greater likelihood of developing neurodegenerative diseases [6, 7]. In the age group 60–74 years, the incidence of CVD is two times higher than in young people, and reaches six times higher at age 75 and more years. This trend is directly related to the increase in mortality due to diseases of the circulatory system [2]. In the Russian Federation, 938,536 deaths were recorded in 2020, compared with 841,207 in 2019 [4]. The high mortality, the increase in the specific burden of comorbid conditions, the aging population, and the increases in the numbers of young and middle-aged people with

genetic mutations create the need to develop a strategy for protective therapy. In the context of nervous system diseases, neuroprotection occupies a special place [8]. In recent years, the concept of "neuroprotection," with clarification of the specific role of brain cells involved in the damage/repair system using animal models, has become a priority for identifying new therapeutic targets [9]. A better understanding of the exact involvement of neurons, glia, and endothelial cells in the pathogenesis of injury gained by comparing results from studies using animal and cell models will provide more opportunities to narrow the existing gap between experimental and clinical data. One of the main directions may be the study of the combined mechanism of action of neuroprotectors [10].

Combined treatment approaches are currently the most attractive therapeutic strategies for the treatment of many disorders, and as the development of ischemia and neurodegeneration involves several factors it is likely that multi-target approaches will be more effective than those focusing on single targets [9]. Employment of drugs should be based on thorough analysis of the correspondence between the clinical and pharmacological effects of a particular drug and the clinical picture in a particular patient, taking account of the patient's age, concomitant pathology, etc. At the same time, it is obligatory to ask: when should a combined agent be used and when should a drug with a broad therapeutic spectrum be preferred? Optimization of the choice of neuropro-

Pirogov Russian National Research Medical University, Russian Ministry of Health, Moscow, Russia; e-mail: profput@mail.ru.

tective therapy regimens in patients with CVD, taking drug synergism into account, is fundamental in clinical practice. Solving this problem requires evaluation of new knowledge on neuroprotection and possible drug synergism. The use of programmed synergism as the basis for rational neuroprotection has promise.

**Neuroprotection as a Drug Strategy.** Pharmacological action in any form of brain damage should be maximally combined and should seek not only to restore normal blood flow in the affected area, but also to eliminate the set of metabolic, transmitter, neurotrophic, and neuroinflammatory reactions that determine the development of neurodegenerative changes in neurons, with resultant neurological deficit. Neuroprotection in a broad sense is the continuous adaptation of a neuron to new functional conditions when damaged by various pathological factors, including neurodegeneration [11–13]. This process can be activated in various ways (drug or non-drug), both before disease onset (the preventive strategy) and during disease progression to prevent damage from spreading (the therapeutic strategy); thus, neuroprotection is regarded as a disease-modifying agent delaying and even terminating progression of pathology.

In the case of drug-induced neuroprotection, the most widely used agents are those affecting neurotransmitter systems and trophic support of cells. In harmful conditions (ischemia, hypoxia, infection, trauma), the number of inactive receptors increases, connections via voltage-gated potassium channels are disrupted, and microglial cells are activated [14, 15]. The active status of microglia is accompanied by the release of various cytokines (TNF, IL-1$\beta$, IL-6, IFN-$\gamma$), increases in levels of reactive oxygen species, and activation of the enzymes nicotinamide adenine dinucleotide phosphate-H-oxidase, and cyclooxygenases-1 and -2. These biological substrates cause secondary damage to brain structures. An excess of glutamate induces the movement of microglia towards damaged neurons and activates NMDA receptors, the entry of $Ca^{2+}$ ions into cells, and adenosine triphosphate (ATP) release [14]. Blockade of $K^+$ channels reduces release of pro-inflammatory cytokine IL-1$\beta$ from activated microglia, decreasing inflammasomes. Neurogenesis is inhibited by decreases in the activity of adenosine A2A and purinergic P2Y1 receptors and impaired stimulation of adenosine A1 receptors and purinergic P2Y13 and P2X7 receptors. Adenosine is a product of the enzymatic breakdown of extra- and intracellular nucleotides adenine and S-adenosylhomocysteine and is involved in regulating vascular tone, inflammation, and immune responses, and is also linked with the processes of thrombosis and angiogenesis [14]. During hypoxia, vasodilation is mediated by A2A and A2B receptors expressed on the endothelium and vascular smooth myocytes. NO synthesis and interactions between A2A receptors and voltage-gated $K^+$ channels enhance the vasodilating effect of adenosine. At the same time, activation of A1 receptors during cerebral ischemia has a marked neuroprotective effect. A2A and A3 receptor

agonists limit leukocyte infiltration and neuroinflammation in the first hours/days after ischemia.

In clinical practice, the use of selective adenosine receptor agonists as neuroprotectors is accompanied by the development of undesirable peripheral effects (the so-called adenosine reactions) [13]. A2A receptor antagonists also protect brain cells, but by reducing excitotoxicity. The pharmacological effects of antagonists are due to the elimination or weakening of the actions of endogenous agonists of these receptors. If antagonists occupy the same binding sites as agonists, then they can displace each other from the receptor-bound state, which can neutralize the pharmacological effect of the drug. Adenosine release activates specific membrane-protective purinergic P2 receptors, which are associated with many functions, including neural stem cell proliferation and migration, vascular reactivity, apoptosis, cytokine secretion, learning and memory, and motor and feeding behavior [16]. Activation of these receptors is partly due to ATP release associated with tissue injury.

Two classes of P2 receptors are recognized: P2X, which are ligand-binding cation channels which function in the control of microglial phagocytosis, and P2Y, which are receptors coupled with G-proteins. Increases in P2Y6 receptor protein expression disrupts normal membrane phosphorylation, enhancing the harmful effects of pathogenic factors [14, 15]. Selective agonists of these receptors suppress phagocytosis and enhance apoptosis and demyelination of neurons. Changes in P2 receptor expression in response to damage cannot currently be linked unambiguously with pathogenetic mechanisms, as in some cases they can stimulate compensatory processes aimed at countering apoptosis.

Considering the complex hierarchical interactions of receptors, enzymes, and carrier proteins, it is difficult to choose a single target for drug-induced neuroprotection; the functional state of the neuron must therefore be corrected using nonspecific actions on a variety of neurotransmitter systems (neuromodulation) [15]. The definition of neuromodulation is flexible and has evolved to describe any kind of neurotransmission that is not directly excitatory (mediated by ionotropic glutamate receptors) or inhibitory (mediated by ionotropic GABA receptors) [15]. There is potential in identifying various neuroprotective effects by means of modulating the receptors for various neurotransmitters. New approaches to pharmacological interventions in neuroprotection processes should be aimed at correcting oxidative stress and inflammation [8]. These effects may be specific to one particular protein (such as a neurotransmitter receptor or a particular cytokine, nuclear factor erythroid-2-related factor 2, or nuclear transcription factor) [13, 16]. Given that addressing a single biological target of neuroprotection limits pharmacological effects and cannot interfere with overall disease progression, the use of drug combinations would appear to be a promising direction [16].

Prescription of combination therapy using multiple neuroprotectors is a difficult but solvable task. Synergism

(Greek σύν – together; ἔργον – work) is a unidirectional interaction of two or more drugs [17, 18]. Varieties of synergism are summation, where simultaneous use of drugs produces a combined effect equal to the sum of the actions of the components of the combination (for example, the simultaneous use of two antioxidant drugs), and potentiation, where the effect of the combination is greater than the sum of the effects of the individual drugs (for example, use of ethylmethylhydroxypyridine succinate (Neuromexol) enhances the effect of benzodiazepine anxiolytics, antiepileptics, and antiparkinsonian (levodopa) drugs) [10, 17, 19]. Unfortunately, modern pharmacology has no unified method for establishing the synergistic spectrum of drug actions which would allow systematic investigation of the effects of drug combinations [17].

Direct synergism is where drugs act on the same substrate (for example, the hypoglycemic effect of insulin is enhanced by synthetic hypoglycemic agents, i.e., sulfonylurea derivatives). Indirect synergism occurs when drugs have different points of application (β2-adrenomimetic and M-anticholinergic bronchodilators). Full synergism is the totality of all effects in combination (inhalation and non-inhalation anesthetics), while incomplete synergy involves summation of only one effect (for example, when chlorpromazine and hypnotics are combined, only the hypnotic effect is enhanced). Sensitizing effects occur when a drug, without affecting the mechanisms of action of another drug, enhances its effects (for example, insulin and glucose stimulate the entry of potassium into cells; vitamin C, when administered simultaneously with iron preparations, increases the plasma iron concentration, etc.).

**Drug Synergism as a Basis for Rational Neuroprotection.** Damage (hypoxia, ischemia) to brain matter increases the permeability of the blood–brain barrier, disrupts circulation in the perivascular spaces, and leads to the development of local inflammation with macrophage activation [20, 21]. Neuroinflammation is a multilevel process characterized by increased production of pro-inflammatory cytokines, along with expression of brain-derived neurotrophic factor and nuclear transcription factor NF-ϰB. At the first stage, this can play a compensatory-adaptive role, though it can go on to enhance glial dysfunction (gliopathy) and neurodegeneration [22]. Gliopathy associated with oxidative and nitrosative stress leads to triggering of autoimmune reactions. Multisystem disorders are activated, including immune, mitochondrial, and endothelial dysfunction. Impairments to metabolic and protein synthesis processes in vessel walls and neurons underlie subsequent morphological damage and development of disease.

Knowledge of fine pharmacodynamic mechanisms allows the optimal combination of drugs to be chosen. The process whereby a physician selects a combination of two or more drugs with the opportunity for potentiation or summation of their neuroprotective effects should avoid polypharmacy, thus reducing the drug load on the patient and

increasing therapeutic efficacy [20]. The main aims of neuroprotection are to increase neuron survival in harmful conditions, to decrease β-amyloid protein synthesis, and to activate neurotransmitter receptors. In clinical practice, antioxidants, neurotransmitters, and drugs that improve neurotrophism are the most widely used.

**Possible Drug Combinations Taking Account of Synergism in Their Actions.** Antioxidants compensate for the pathophysiological effects of hypoxia and ischemia by activating the intracellular antioxidant defense system [23]. Drugs of this class, including combined formulations, have synergistic effects in the form of summation of the effects of all neuroprotectors, such that these combinations can be used in in asthenic and anxiety disorders and mild cognitive impairment. Monotherapy is preferable in young patients, while combined treatment can be used in patients of all ages, including those with sleep disorders, anxiety, and mild cognitive disorders. Specific anti-dementia drugs are preferred in severe cognitive impairment, noting that their effects can be enhanced by antioxidants [10, 24].

In rehabilitation after vascular accidents and injuries, combinations of neurotrophic drugs and antioxidants are advisable; these can probably save neurons, stimulate the growth of axons and dendrites, and form new connections [25, 26]. In severe neurological deficits and neurodegenerative and inflammatory lesions, a different pharmacological approach is needed to stimulate the regeneration of damaged neurons, with restoration of the brain-derived neurotrophic factor (BDNF)-dependent tropomyosin-tyrosine kinase receptor (TrkB) pathway, which is an important mechanism for the survival of mature neurons. The absence of BDNF increases the expression of several genes encoding a group of enzymes forming the basis of antioxidant defense and the systems activating, differentiating, and mediating the effector functions of inflammatory T cells and inflammasomes [23]. The TrkB pathway and the nuclear erythroid factor signaling system are potential targets for neuron survival and the initiation of the regeneration of damaged neurons and synaptic connections. Some modulators have been described which can activate antioxidant defense and cell survival systems mediated by neurotrophin signaling [24]. Certain small non-neurotrophin peptides specifically interact with the corresponding receptors to stimulate the synthesis of releasing factors [25].

**Neuropeptide and Neurotransmitter Preparations.** Neuropeptide preparations consisting of small molecules are capable of selective binding to endogenous proteins [24–26]. Structural transformations triggered by various stimuli contribute to the therapeutic use of peptide complexes [26]. Peptides penetrate the blood–brain barrier (BBB) and have neurotrophic, mediator, and anti-inflammatory properties [25]. In recent years, a therapeutic strategy has been developed for "minipeptides," compounds that can selectively bind to p75NTR and Trk receptors, increasing their neurotrophic activity. Experimental studies have

shown that systemic administration of peptides for five weeks to elderly mice improved spatial memory, decreased the size of amyloid plaques, and reduced the severity of neuroinflammation [27]. So-called SMART peptides have a special role, due to their high selectivity, efficacy, and safety [26]. SMART peptides can be used as substances potentiating the actions of other drugs and promoting the transfer of other drugs across the BBB [24].

In clinical practice, the use of neuropeptides in various neurological pathologies leads to summation of therapeutic effects with those of antioxidants and potentiation of the actions of neurotransmitters, stimulating neuromodulation processes. Data have been obtained indicating that lower doses of Cortexin have been used in experiments as compared with Cerebrolysin and Actovegin, due to its higher efficacy, such that this drug is promising in terms of synergism [28]. The results of the CORTEX multicenter clinical and epidemiological observational program led to the conclusion that Cortexin has high clinical efficacy in correcting asthenic and cognitive impairments in patients with postcovid syndrome [29].

Cortexin, a multicomponent peptide drug with an optimally balanced composition, is also effective in the treatment of other neurological diseases [30]. Cortexin effects are apparent by treatment day 10–14 and last up to one month; dose-dependent effects are seen in relation to a number of symptoms, especially when the dose is increased to 20 mg [29]. Cortexin, affecting ionotropic and metabotropic glutamate and GABAergic receptors, prevents excitotoxicity and helps optimize the processes of excitation and inhibition, which is clinically significant for patients with chronic cerebral ischemia, headache, and other syndromes [29, 30]. The drug has systemic and local anti-inflammatory effects, significantly reducing IL-1 and TNF levels [3, 32]. Cytoskeletal proteins interacting with Cortexin form tight junctions in vascular endothelial cells, helping to preserve the integrity of the BBB [27]. An example of an unwanted synergism is provided by simultaneous administration of Cortexin and other neurotrophic drugs, which results in competition for ligands and the risk of allergic reactions. Cortexin increases the effects of antidementia and antiepileptic drugs, as well as antidepressants.

Citicoline (Recognan) is a drug involved as an intermediate in major metabolic pathways in the brain and is a key element in phosphatidylcholine synthesis. It is made up of cytidine and choline linked by a diphosphate bridge. Cytidine is a nucleotide formed by the combination of cytosine with ribose with a β-N1-glycoside bond. Choline is the basis for acetylcholine formation, stimulates tyrosine hydroxylase activity, increases noradrenaline (in the cortex and hypothalamus), dopamine (in the striatum), and serotonin (in the cortex, striatum and hippocampus) levels, as well as dopamine secretion [33, 34]. Activation of dopaminergic transmission is required in the process of switching from one cognitive process to another and its insufficiency leads to inertia in patients, with slowing of cognitive processes [35]. Compliance

with treatment with citicoline (Recognan) treatment is enhanced by use of a solution for drinking, a convenient dosage regime (once daily), and the absence of a dose-dependent effect. This point is particularly relevant for elderly (reducing the risk of polypharmacy) and young (lack of complex regimens with a rapid onset of effect) patients.

Citicoline (Recognan), like Cortexin, promotes inhibition of apoptosis and supports energy metabolism, helps modulate neurotransmission, increases vasodilation, suppresses inflammation, improves glucose metabolism, and has antioxidant actions [34, 35]. Citicoline (Recognan) can reduce β-amyloid deposition in the brain, it can probably stimulate the redistribution of the main glutamate transporter EAAT2 into lipid raft microdomains, leading to increased glutamate uptake, which is clinically manifest as improved cognitive functions [34, 35]. Citicoline (Recognan) reduces the severity of delayed ischemic damage to the hippocampus, which is functionally significant for the development of dementia. Cortexin complements citicoline (Recognan) to the greatest extent in relation to activation of Trk receptors in regenerative signaling cascades and anti-inflammatory effects. The greatest levels of synergism can be obtained with respect to neuroprotective activity, modulation of neurotransmission, and neurotrophic and anti-inflammatory effects. Citicoline (Recognan) can be used for up to 6 months. The combination is recommended for middle-aged and elderly patients with marked neurological symptoms, cognitive impairment, damage to the extrapyramidal system, gait disorders, postural instability, and cochleovestibular syndrome [36]. It can be used in severe somatic pathology, in the acute phase of stroke, including at the prehospital stage. Citicoline (Recognan) increases the effects of anti-dementia drugs and levodopa, so it can be prescribed to patients with neurodegenerative diseases, including Parkinson's disease, to reduce the dose of levodopa-containing drugs.

**Conclusions.** The challenge of neuron protection and adaptation is extremely difficult, as post-damage excitotoxicity, apoptosis, inflammatory responses, etc., hinder repair processes. A deeper understanding of the involvement of neurons, glia and endothelial cells should provide the key to developing new therapeutic strategies. One promising direction consists of studying synergism in drug actions, which may be of decisive importance for increasing treatment efficacy and reducing the risk of polypharmacy. The search for new optimal synergistic combinations may become an important direction in neuroprotection.

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