

THE DEPARTMENT OF NEUROCHEMISTRY FROM 1925 UNTILL THE PRESENT DAY

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Activity in the Department of Neurochemistry from 1925 until the present day was described in particular. The main scientific areas of research at the Department of Biochemistry of the Nervous System until 1982 were following: study of the chemical topography of the nervous system; study of subcellular and suborganoid localization of neurospecific proteins; investigation of the effect of psychotropic agents on nitrogen, carbohydrate, and protein metabolism in the structures of the nervous system; studying membrane organization and function mechanisms of enzyme systems for active transport of sodium, potassium, and calcium in nerve cells. Since 1982, research in the Department has been focused primarily on the following areas: biogenesis of membrane and secretory proteins; research on neurospecific proteins; research on plasma membrane directly involved in the generation and transmission of nerve signals. Since 2010, the research of the Department of Neurochemistry was aimed at solving the following urgent problems: elucidation of the role of structural organization of membrane and lipid- protein interactions in the regulation of nerve signal transmission process; elucidation of the role of presynaptic receptors in the regulation of key stages of neurotransmission process and determination of the ways to modulate the neurotransmitter reception system; search and identification of natural membranotropic and neuroactive compounds, analysis of the molecular mechanisms of existing membranotropic and neuroactive drugs action; space biology, namely the development of a method for determining the toxicity of planetary dust; nanotechnology, namely the synthesis and analysis of the neuroactive effect of nanoparticles; environmental neurotoxicology, namely the study of the neurotoxic effects of environmental pollutants and the development of the ways to overcome their harmful impact.

Key words: *synaptic neurotransmission, nerve terminals, exocytosis, neurotransmitter transporters, receptors, membranotropic and neuroactive compounds, functional nanocomposites and nanohybrids.*

Since the founding of the Ukrainian Biochemical Institute of the People's Commissariat of Education of the Ukrainian SSR (1925), and later the Institute of Biochemistry of the National Academy of Sciences of Ukraine, one of its main scientific directions was the biochemical study of the nervous system. In 1935, the Laboratory of Neuromuscular Activity was founded. After that, in 1944, the Laboratory of Biochemistry of the Nervous System was created on its basis, and in 1966, the laboratory acquired the status of the Department of Biochemistry of the Nervous System. In 1982, the Department of Biochemistry of the Nervous System was merged with the Laboratory of Biomembranes, and the new Department was named the Department of Neurochemistry.

The supervisor of this research was the Director of the Institute and simultaneously the Head of the Department of Biochemistry of the Nervous System, academician of the Academy of Sciences of the USSR and the Academy of Sciences of the Ukrainian SSR, Olexandr Volodymyrovych Palladin (1925–1972). Subsequently, research in the field of neurochemistry was led by D. Sc. Yakiv Vasylovych Belik (1973–1982), Academician of the Academy of Sciences of Ukrainian SSR Valeriy Kazymyrovych Lishko (1983–1991), Ph.D. Nina Germanivna Himmelreich (1991–2013), and since 2013 until now, Professor, D.Sc. Tetiana Olexandrivna Borisova.

The main scientific areas of research at the Department of Biochemistry of the Nervous System until 1982 were the following:



O. V. Palladin



Ya. V. Belik



N. H. Himmelreich



T. O. Borisova

- study of the chemical topography of the nervous system, i.e. determining the specific chemical composition and the course of biochemical processes in morphologically and functionally different parts of the central and peripheral nervous system (O. V. Palladin, G. Ya. Gorodyska, O. Ya. Rashba, E. B. Skvyrska, B. Y. Khaikina);

- study of subcellular and suborganoid localization of neurospecific proteins, as well as the study of the functioning of enzyme systems of carbohydrate-phosphorus, lipid, and protein metabolism in morphologically and functionally different structures of nervous tissue (O. Ya. Rashba, E. B. Skvyrska, B. Y. Khaikina, N. M. Polyakova, Ya. V. Belik, T. P. Babi, K. O. Goncharova, Ts. M. Shtutman, O. N. Fedorov, V. I. Tyulenev, L. A. Tsaryuk, V. K. Lishko, S. O. Kudinov);

- investigation of the effect of psychotropic agents on nitrogen, carbohydrate, and protein metabolism in the structures of the nervous system (Ya. T. Terletska, V. Y. Kocherga, L. S. Smerchynska, K. O. Goncharova, A. O. Musialkovska, P. K. Parkhomets);

- studying membrane organization and function mechanisms of enzyme systems for active transport of sodium, potassium, and calcium in nerve cells (O. V. Palladin, O. V. Kirshenko, V. K. Lishko, S. A. Kudinov, O. M. Rozhmanova, N. M. Polyakova, G. L. Vavilova, M. K. Malysheva, V. I. Nazarenko, O. V. Kravtsov).

Since 1982, research in the Department has been conducted mainly in the following areas:

- biogenesis of membrane and secretory proteins;

- research on neurospecific proteins;

- research on plasma membrane systems directly involved in the generation and transmission of nerve signals.

In particular, research was focused on:

- channel-forming activity of a specific hydrophilic tetrodotoxin (TTX)-sensitive protein and properties of TTX-sensitive channels in planar bilayer lipid membranes and liposomes (V. K. Lishko, M. K. Malysheva, A. V. Stefanov, N. G. Himmelreich, L. G. Storchak);

- mechanisms of protein inclusion into lipid membranes and protein transport across membranes (V. K. Lishko, D. I. Balkov, G. V. Los, T. O. Borisova);

- mechanisms of ion channels formation by neurotoxins in planar lipid bilayers and lipid vesicles and studying properties of these channels (V. K. Lishko, V. Yu. Sokolov, I. O. Triakash, A. M. Chanturia, O. Ya. Shatursky);

- presynaptic mechanisms of action of the toxin from the venom of black widow spider *Latrodectus mactans tredecimguttatus*, α -latrotoxin, and its impact on the brain nerve terminals (N. H. Himmelreich, Ya. T. Terletska, L. G. Storchak, N. G. Pozdnyakova); importantly, since the 1980s and for the next 30 years, the Department studied the neuroactive properties of α -latrotoxin;

- the fusogenic activity of α -latrotoxin (Ya. T. Terletska, I. O. Triakash).

It has been shown that hydrophilic proteins from brain and muscle tissue can spontaneously interact with phospholipid bilayers and liposomes to form TTX-sensitive sodium channels. When a TTX-sensitive protein is incorporated into a liposomal membrane, a channel with an asymmetric structure

is formed. The specific effect on the sodium permeability of the channel by the modulators of endogenous sodium channel activity, veratridine and tetrodotoxin, led to the conclusion that a hydrophilic precursor of the sodium channel exists.

In the research of neurospecific proteins, the main attention was paid to the S-100, 14-3-2 and myelin basic protein. Immunochemical methods established the localization of these proteins in nervous tissue as well as changes in their content during brain injuries and pathologies. Thanks to the development of a method for obtaining a pure preparation of the basic protein from the myelin sheath of the brain white matter, experiments were conducted to study the effect of administering this protein to experimental animals, and it was found that it caused allergic encephalomyelitis. The therapeutic effect of high doses of myelin on experimentally induced allergic encephalomyelitis was established (Ya. V. Belik, Ya. T. Terletska, O. P. Kozulina, L. P. Syrovatska).

In studies of nervous tissue proteins, whose function is to ensure active transport of ions, the main attention was paid to Mg^{2+} , Na^+ , K^+ - and Mg^{2+} , Ca^{2+} -activated ATPases - enzymes that provide the specificity of the ionic composition of a nerve cell. Experiments were conducted to establish the localization of ATPases in different parts of the nervous system. The peculiarities of ATPase systems in peripheral nerves functioning under normal conditions and during the development of degenerative processes were studied. The mechanism of interaction of Mg^{2+} , Na^+ , K^+ -ATPase with ouabain and local anesthetics and the role of the lipid environment in the functioning of this enzyme were determined. A significant attention in these studies was devoted to the assessment of the ATP hydrolysis mechanism itself, which is a complex reaction in which Na^+ , K^+ and Mg^{2+} ions participate (O. V. Kirsenko, V. K. Lishko, S. O. Kudinov, V. Y. Kocherga, V. I. Nazarenko, G. L. Vavilova, O. V. Kravtsov).

Using a model system of cotranslational translocation, consisting of liposomes and a cell-free protein synthesis system, it was shown that liposomes can serve as acceptors of synthesized membrane/secretory proteins. The latter cotranslationally cross the phospholipid membrane bypassing the facilitating translocation protein system. The important role of the signal peptide in the transport process was also established (T. O. Borisova, I. O. Triakash, V. K. Lishko) [1].

The ability of α -latrotoxin to induce calcium conductivity in planar lipid bilayers (BLM) has been shown. Ion channels formed by the toxin in the BLM have been characterized. The potential-dependent nature of the channel formation process and the vectorial nature of the process of incorporating the α -latrotoxin molecule into the bilayer have been shown. The asymmetric form of α -latrotoxin channels has been proven by analyzing the current-voltage characteristics. High cation specificity of the channels has been established [2]. The interaction of α -latrotoxin with nerve terminals (synaptosomes) was studied, in particular the process of binding and internalization of α -latrotoxin by synaptosomes, properties of ion channels formed by α -latrotoxin in the plasmalemma of synaptosomes, relationship and interdependence between the ability of α -latrotoxin to form ion channels and stimulate the release of neurotransmitters from nerve terminals and the role of the processes of phosphorylation and dephosphorylation of neuronal proteins in the implementation of the secretogenic function of α -latrotoxin were investigated. Using various model systems, the ability of the α -latrotoxin molecule to fuse membrane structures was established, i.e., the fusogenic activity of the toxin was shown. The dependence of fusogenic activity on the degree of protonation and hydrophobicity of the α -latrotoxin molecule was established [3-6].

A system for modeling the process of neurosecretion, consisting of synaptic vesicles and plasma membranes of the brain nerve terminals, has been developed. The stimulating effect of MgATP on the fusion process of these structures and its sensitivity to physiological concentrations of calcium have been shown [7].

A new dosage form for acute and chronic forms of pneumonia, bronchial asthma, cystic fibrosis and other lesions of the lung tissue treatment has been developed. A patent for "Method of obtaining an antihypoxic drug in liposomal form" has been obtained.

Since 2010, the Department of Neurochemistry has been conducting studies of molecular mechanisms of disorders in excitatory and inhibitory neurotransmitters transport under pathological conditions and under conditions of excitotoxicity in presynaptic nerve terminals of the brain. The complex modulation of synaptic transmission in brain nerve terminals by new agents for theranostics of neuropathologies was studied. The research was aimed at solving the following urgent problems:

- elucidation of the role of structural organization of membrane and lipid-protein interactions in the regulation of the nerve signal transmission process;
- elucidation of the role of presynaptic receptors in the regulation of key stages of the neurotransmission process and determination of the ways to modulate the neurotransmitter reception system;
- search and identification of natural membranotropic and neuroactive compounds, analysis of the molecular mechanisms of existing membranotropic and neuroactive drugs' action;
- space biology, namely the development of a method for determining the toxicity of planetary dust;
- nanotechnology, namely the synthesis and analysis of the neuroactive effect of nanoparticles;
- environmental neurotoxicology, namely the study of the neurotoxic effects of environmental pollutants and the development of ways to overcome their harmful impact.

The plasticity of synaptic processes is achieved due to systems of precise modulation of key stages of the neurotransmission process - the release of neurotransmitters into the synaptic cleft and active reuptake of neurotransmitters from the synaptic cleft. The understanding of biochemical mechanisms of the modulation of these processes is extremely insufficient, therefore, the main focus of the research was aimed to study the pathways and mechanisms that underlie modulatory processes and ensure the maintenance of a balance between excitation and inhibition. Using appropriate methods of analysis (radioisotope analysis, fluorescence spectrometry, laser correlation spectroscopy, confocal microscopy, flow cytometry, method of recording ionic conductivity of a bilayer lipid membrane), a cell-free system for studying the process of exocytosis and experimental models as hypergravity loading; early age hypoxia accompanied by seizures; cholesterol deficiency, which is inherent in a number of diseases accompanied by the development of neuropathologies, made it possible to find out which presynaptic processes play the key role in the development of neuropathologies [8-17].

Using various model systems of hypoxia and excitotoxicity conditions, an analysis of compensatory mechanisms was performed. Activation of these mechanisms allows to balance neuronal activity and to investigate the multidirectional effects of existing neuroactive drugs and new synthesized neuroactive compounds on the neurotransmission process.

Early age hypoxia is one of the crucial factors in mental retardation development, and, in severe cases, epilepsy, resistant to drug treatment. It has been shown that hypoxia and seizures in rats during the perinatal period caused changes in the implementation of energy processes. A persistent and long-term consequence of perinatal hypoxia was an increase in the level of extracellular GABA. Normalization of the level of extracellular GABA is possible with an increase in the level of ATP in the terminals, which occurs under the conditions of consumption of pyruvate by the terminals of cortical and hippocampal neurons as the only energy substrate [18].

Changes in the ratio of active GABA transporters GAT1/GAT3 expressed in the plasma membrane of nerve terminals after perinatal hypoxia and the possibility of modulating their activity in different parts of the brain with β -alanine have been shown [9]. Age- and hypoxia-dependent reduction in [3 H]GABA uptake was found in the rat hippocampus, thus establishing the particular vulnerability of this structure to hypoxia compared to the cortex and thalamus [20].

Activation of receptors located on presynaptic terminals is one of the main pathways for fine regulation of the neurotransmission process. Presynaptic ionotropic receptors activated by glutamate, a mediator of the excitation signalling, are involved in the regulation of inhibitory processes in the presynapse by inducing synchronous and asynchronous exocytosis, triggered by the inflow of Na^+ and Ca^{2+} into the nerve terminal mediated by receptor ion channels. The key link in the signaling pathway between receptor activation and exocytosis is stimulation of reactive oxygen species (ROS) production. The leading role of AMPA/kainate receptors in the process of stimulating the generation of ROS and the role of NADP oxidase in the signaling pathway of NMDA receptors have been shown [21].

Studies in a cell-free system of action of the antiepileptic drug levetiracetam, a specific ligand of the transmembrane protein of synaptic vesicles SV2, indicated the involvement of the SV2 protein in both the processes of homo- and heterotypic fusion, and in the clustering of synaptic vesicles. Using levetiracetam, it was shown that SV2A functioned as a regulator of the process of clustering of synaptic vesicles and calcium-regulated fusion of vesicles with the plasma membranes of synaptosomes. Levetiracetam activated the process of calcium-regulated

release of GABA from nerve terminals of the cortex, hippocampus and thalamus of the rat brain. The effectiveness of levetiracetam was significantly higher in animals exposed to perinatal hypoxia [22].

It has been shown that amphotericin B, as well as recombinant subunit B of diphtheria toxoid, when added to only one side of a “planar cholesterol-containing phospholipid bilayer membrane (thickness ~51 Å), were capable of forming long-lived ion channels in the open state, in the formation of which the length of the acyl tails of fatty acid residues of phospholipid molecules plays a critical role. In the bilayer phospholipid membrane, the properties of the channels formed by calixarene C-99 allowed us to consider it as a potential-dependent anion transporter [23, 24].

In the Department, research in the field of space biology has also been conducted. Gravitational overload, which is an inevitable factor of space flights, caused significant changes in neuronal processes, in particular in the regulation of the release and accumulation of the excitatory mediator – glutamate in presynaptic terminals. It was found that under conditions of gravitational loading of animals, significant changes occurred in the processes of glutamate release from presynaptic nerve terminals: Ca^{2+} -dependent release of glutamate from synaptosomes decreased due to a decrease in the content of the neurotransmitter in synaptic vesicles, and the cytosolic level of glutamate increased, which indicated a redistribution of the neurotransmitter between the vesicular and cytosolic pools due to the action of hypergravity [25]. A unique effect of the Lunar dust simulant in comparison with the Martian dust simulant and synthesized magnetite nanoparticles has been shown, namely, an increase in the binding of glutamate to nerve terminals. By causing changes in the extracellular level of glutamate, which is extremely important for proper synaptic transmission, Lunar dust can have a detrimental effect on the homeostasis of this neurotransmitter in the central nervous system [26].

The molecular mechanisms of action of magnetic nanoparticles of natural origin, coated with a protein shell, ferritin, and the specific effects of the protein and inorganic components of this natural nanoparticle have been discovered, which allowed the use of ferritin for the modulation of neurotransmitter transport in the nerve terminals of the brain [27].

The neuromodulatory properties of carbon dots synthesized from beta-alanine have been discovered,

namely, a significant inhibition of the active accumulation of GABA by the nerve terminals of the rat brain was revealed. The neuroactivity of carbon dots makes them capable of modulating the process of synaptic transmission simultaneously with the visualization of the studied processes [28-31].

All of the above-mentioned results of the Department's work have become the scientific basis for creating a concept regarding the molecular mechanisms of regulation of active transport and reception of neurotransmitters in the presynapse.

Over the past 5 years, starting from 2020, the Department has initiated research and obtained new scientific results aimed at preserving the state of the environment. The constant increase in the number of patients with neurological diseases is a global and still unresolved problem of modern society. There is increasing evidence of the relationship between environmental metal pollution and the etiology of neurological diseases at an early age (for example, autism), or in old age (e.g. Alzheimer's disease). Environmental pollutants, in particular neurotoxic heavy metals, act as a complex mixture [32]. Military operations lead to a significant increase in pollution with neurotoxic metals and the concentration of neurotoxic particulate matter in the air, which in turn also contributes to significant environmental pollution. In this context, for an adequate assessment of the risk of neurotoxicity, the effect of heavy metals in their multi-pollutant mixture should be investigated. This approach was developed and successfully used in the Department to study the effect of carbon-containing smoke particulate matter and heavy metals on the main characteristics of synaptic transmission.

In addition, post-traumatic stress disorder that occurs in the population during martial law and military operations significantly exacerbates this problem. Prevention of the development and successful treatment of neurological diseases is the most urgent scientific task, the successful solution of which is hampered by the lack of fundamental and applied knowledge regarding the regulation of key processes of synaptic transmission in the central nervous system.

The Department has developed a new methodology, obtained and characterized a panel of water-suspended preparations of carbon-containing smoke particles from the combustion of materials of natural and anthropogenic origin (Fig. 1 and 2). The presence of nanosized particles in the preparations

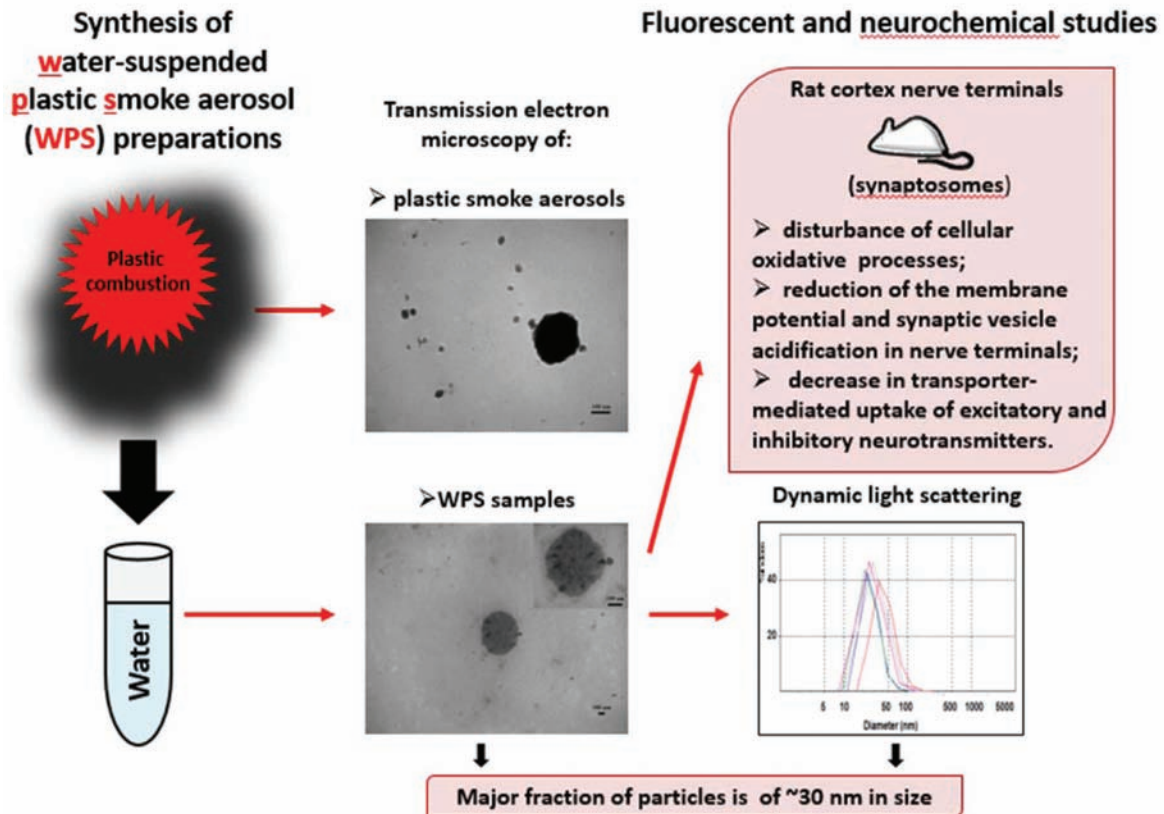


Fig. 1. Methodology for obtaining water-suspended preparations of carbon-containing smoke particles from plastic combustion [33]

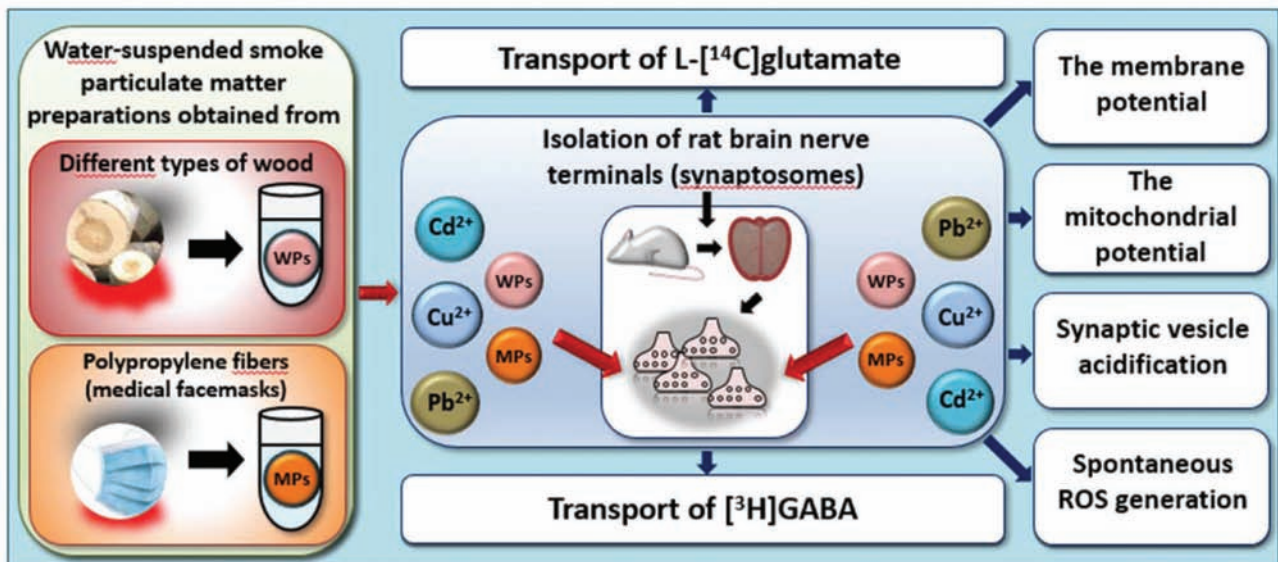


Fig. 2. Experimental design to study the neurological hazards of multi-pollution by cadmium, lead, copper, and smoke particulate matter from burning of wood and medical masks [36, 37, 40]

of smoke aerosols from the combustion of wood and plastic has been shown, and it has been proven that they disrupt the process of synaptic transmission and cause an imbalance of excitation-inhibition processes in the brain nerve terminals. The unique optical properties of the particles can be used in “smart” monitoring of air pollution. The results obtained on the neurotoxicity of smoke from burning plastics were published in 2020 [33-35].

For the first time, a decrease in the membrane potential of nerve terminals and isolated neurons, mitochondrial potential, and acidification of synaptic vesicles under the action of smoke preparations from the combustion of medical masks has been demonstrated in the frame of NRFU project 2020.02/0147 (PI - Head of the Department, Prof., D.Sc. T. Borisova). It has been proven for the first time that smoke preparations of both natural and anthropogenic origin have neurotoxic properties and can provoke a malfunction in the presynapse due to the weakening of the transporter-mediated uptake of glutamate/GABA by nerve terminals, disrupt the balance of excitatory and inhibitory neurotransmission, which proves the connection between air pollution by particulate matter and nervous system disorders and neurodegenerative diseases. ROS generation was weakened in the presence of smoke components from the combustion of both wood and plastic. The disposal of waste disposable medical masks by incineration led to the release of neuroactive nanosized solid particles into the environment, contributing to the pollution of air and water resources with nanoplastics, as well as the development and spread of neuropathologies. [36].

It has been shown for the first time that the increase in extracellular levels of excitatory (glutamate) and inhibitory (gamma-aminobutyric acid, GABA) neurotransmitters, the decrease in the release of neurotransmitters by exocytosis, and the change in the membrane potential of nerve terminals in the presence of smoke preparations of natural and anthropogenic origin were associated with the creation of single ion-conducting pores in the planar lipid bilayer.

A comparative analysis of the neuroactive effect of smoke preparations from wood and plastic combustion revealed a fundamental difference associated with a decrease in synaptic inhibition due to a decrease in synaptosomal extracellular level of GABA under the influence of smoke from plastic combustion. This may be the cause of the develop-

ment of neuropathology in response to air pollution with solid particles from plastic combustion and can be used in predicting health risks during man-made disasters [35].

It has been shown for the first time that preparations of smoke particles from the combustion of various types of wood differed from each other in their characteristics. Solid smoke particles from the combustion of different types of wood differently affect the release of glutamate and GABA from nerve terminals. Solid smoke particles from poplar wood were found to be the most neurotoxic and caused a more than fivefold increase in the extracellular level of the excitatory neurotransmitter glutamate, disrupted the release of neurotransmitters by exocytosis, caused membrane depolarization in nerve terminals, which, in turn, cause the development of excitotoxicity and leads to neurological consequences due to a violation of the balance of excitation and inhibition in the central nervous system [34].

For the first time in the frame of NRFU project 2021.01/0061 (PI - Head of the Department, Prof., D.Sc. T. Borisova), the combined neurotoxic effect of Pb^{2+} and solid carbonaceous smoke particles from combustion of wood and medical masks on nerve terminals has been proven. It has been shown that smoke preparations did not change the Pb^{2+} -induced increase in extracellular levels of glutamate and GABA, thereby demonstrating an additive effect and the absence of interference of the neurotoxic effects of Pb^{2+} and solid smoke particles. Both smoke preparations reduced the Cd^{2+} -induced increase in extracellular levels of glutamate and GABA in nerve terminals. In fluorimetric measurements, metals and smoke preparations demonstrated an additive effect on the membrane potential of nerve terminals, causing membrane depolarization. Thus, the diversity of the interference effects of pollutants, namely heavy metals and solid smoke particles, on key presynaptic processes was revealed. The reciprocal neurological danger of multi-pollution with cadmium and lead on the one hand and solid smoke particles from burning poplar wood and medical masks on the other hand has been proven due to the disruption of the excitation-inhibition balance and the membrane potential of nerve terminals [37].

The combined use of mercury and carbonaceous particles (carbon dots), as models of air pollutant particles, has been shown to attenuate acute mercury-induced neurotoxicity in nerve terminals. These carbon dots and Hg^{2+} acted as a complex in

nerve terminals, as confirmed by fluorimetric data on changes in their spectroscopic characteristics in the presence of Hg^{2+} [38].

Copper is one of the main pollutants of the territory of Ukraine during active military operations. Copper is an indispensable transition metal, necessary for several important biological processes, however, its excess is toxic to cells. Excessive consumption of copper and disruption of copper homeostasis regulation cause its accumulation in the brain, and excess copper causes memory deficits and cognitive impairment. It is known that environmental influences and/or changes in copper homeostasis contribute to the development of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [39]. The ability of Cu^{2+} to influence neurotoxicity induced by water-suspended wood smoke particulate matter (PM), and vice versa, was investigated using rat presynaptic nerve terminals from the cerebral cortex. The interaction of Cu^{2+} and PM, changes in particle size and surface properties were shown in the presence of Cu^{2+} by microscopy, DLS and IR spectroscopy. Both Cu^{2+} and PM alone increased the levels of the excitatory neurotransmitter L-[^{14}C]glutamate and the inhibitory [^3H]GABA in nerve terminal preparations. When co-administered, Cu^{2+} significantly enhanced the PM-induced increase in the levels of both neurotransmitters in the synaptosomal preparation, thereby demonstrat-

ing a cumulative synergistic effect and significant interference of the neurotoxic threat associated with Cu^{2+} and PM. In fluorimetric measurements, Cu^{2+} and PM also demonstrated a cumulative synergistic effect on membrane potential, mitochondrial potential, synaptic vesicle acidification, and spontaneous generation of ROS. Thus, a synergistic effect of Cu^{2+} and PM on key presynaptic processes and a multi-pollutant neurological threat through disruption of the excitatory-inhibitory balance, membrane and mitochondrial potential, vesicle acidification, and generation of reactive oxygen species was demonstrated [40].

It has been proven that solid carbonaceous smoke particles - air pollutants - can be carriers of enveloped SARS-Cov-2 viral particles to the brain and enhance their neurotoxic effects (Fig. 3). The international publication of these results was included in the top 25% of research results, assessed by the Springer publishing house "Altmetric", has 23 citations in the Web of Science database, 27 citations in CrossRef [41].

Recently, the prospects of using agricultural waste to create carbon nanomaterials have gained great interest around the world. Accumulation of agricultural waste damages the environment, raising the need for its recycling. It is a promising source for the production of valuable products that require fewer chemical reagents ("green principles") [42].

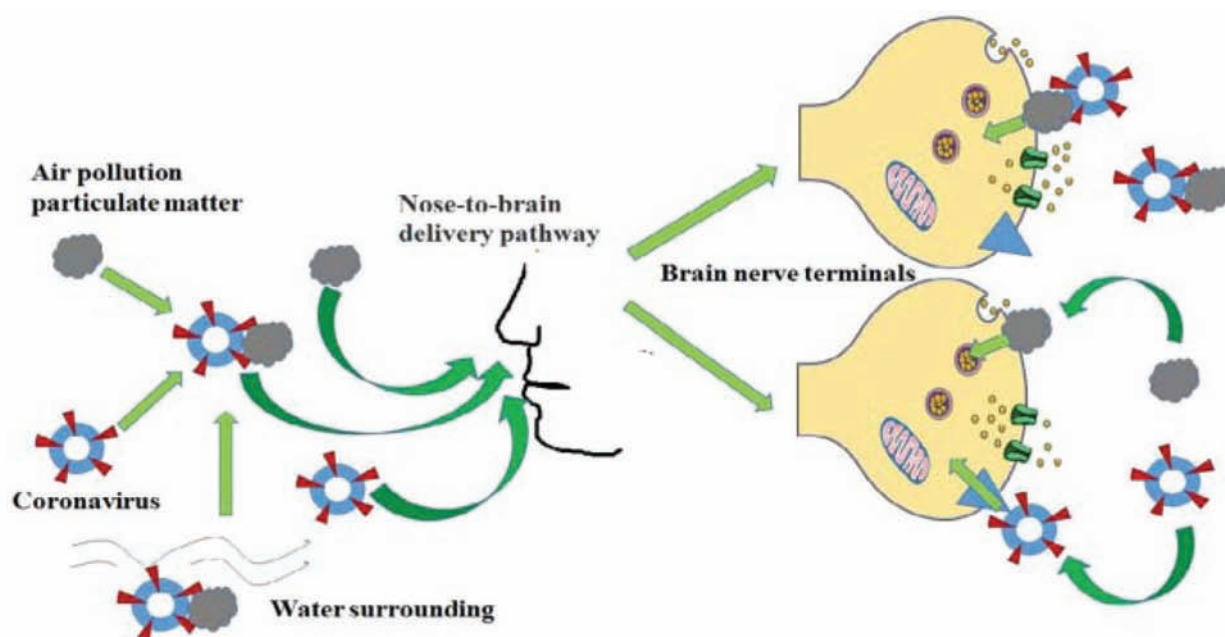


Fig. 3. Solid carbonaceous smoke particles – air pollutants can be carriers of enveloped SARS-Cov-2 viral particles to the brain and enhance their neurotoxic effects [41]

In recent years, carbon dots (CDs) have attracted much attention due to their unique properties, such as high biocompatibility, low toxicity, nano-size, etc. [43, 44]. High-quality CDs can be synthesized using biomass and “green” approaches; however, this issue still remains unclear and awaits resolution.

Recently, it was proposed within the framework of the NRFU project 2023.03/0036, “Functionalized carbon-based nanomaterials obtained by “green methods” from Ukrainian agricultural wastes to overcome multilevel neurotoxicity under the action of xenobiotic/biologically important transition metals and arsenic” (PI - N. Krisanova) to synthesize carbon nanoporous materials and nanoparticles from Ukrainian agricultural wastes that can be used to reduce neurotoxicity caused by heavy metals such as Hg, Pb and Cd, the metalloid As, and biologically important transition metals such as Cu and Fe, in high concentrations, and their multi-pollutant mixture, while preserving synaptic processes controlled by the physiological metal Ca.

Environmental exposure to neurotoxic metals such as Cd, Pb, Hg and metalloid As is a global health concern affecting millions of people worldwide as underlined by the WHO, Ten Chemicals of Public Health Concern, 2020. As, Pb, Hg, and Cd are ranked first, second, third, and seventh, based on their frequency and potential toxicity for human exposure in the priority list of the USA Agency for Toxic Substances and Disease (ATSDR's Substance Priority List). For instance, at least 140 million people in 50 countries have been drinking water containing As at levels above the WHO guideline (WHO Arsenic Fact Sheets, 2018).

Comparative analysis of neurotoxic effects and adsorption capacity of carbon materials, starting from carbon nanoporous micro-sized particles and ending with carbon nanoparticles, has never been carried out before.

These studies are carried out in the Department within the framework of above-mentioned project NRFU 2023.03/0036. Carbon materials were synthesized at the Pisarzhevsky Institute of Physical Chemistry, NAS of Ukraine, Kyiv. It was found that micro- and nanoparticles synthesized using “green” principles by pyrolysis methods from agricultural waste, namely, from dry apples and corn cobs, did not affect the extracellular levels of neurotransmitters glutamate and GABA and the membrane potential of nerve terminals [45]. Carbon particles from dried apples and corn cobs reduced the toxic effects

of Hg, Pb, and Cd on the extracellular levels of the neurotransmitters glutamate and GABA and on the membrane potential of nerve terminals. Due to their biocompatibility and ability to chelate heavy metals, unfunctionalized carbon particles have significant prospects for application in biotechnology, medicine, and ecology.

These data are of particular importance during recovery after military operations, since under these specific conditions, air pollution by solid carbon-containing particles, heavy metals, and their complexes significantly increases. In total, 10 scientific papers were published on this topic during the period 2020-2025 [33, 40, 41, 46, 47].

The Department has been conducting research within the framework of classical neurochemistry. Modulation of synaptic neurotransmission with neuroactive substances and nanoparticles has been carried out.

In particular, in the frame of the Latvia-Ukraine project of MES of Ukraine and classical neuroscience research, the action of the Sig-1 receptor blocker NE-100, which can be used as a pharmacological modulator of GABAergic neurotransmission, was analyzed. It has been established that GABA transport was particularly sensitive to the action of the Sig-1 receptor antagonist NE-100, which caused significant changes at the presynaptic level and can be used as a pharmacological modulator of GABAergic neurotransmission [48].

An approach has been developed to monitor the process of formation of a dynamic glutamate biocorona on the surface of $\gamma\text{-Fe}_2\text{O}_3$ nanoparticles and the components responsible for its desorption have been identified, which can be used for the delivery of glutamate to the nervous system, or for the adsorption of glutamate upon stroke, brain injuries, epilepsy, and cancer treatment with its subsequent removal using a magnetic field, since excessive concentration of extracellular glutamate is a characteristic feature of the above pathologies [49].

Modulation of synaptic neurotransmission by gadolinium-containing nanohybrids was performed. It was proven that gadolinium-containing nanohybrids with proven ability to treat brain metastases did not alter the transporter-dependent accumulation and release of the excitatory neurotransmitter glutamate from nerve terminals in the rat brain, which indicated the absence of their neurotoxicity [50] (Fig. 4).

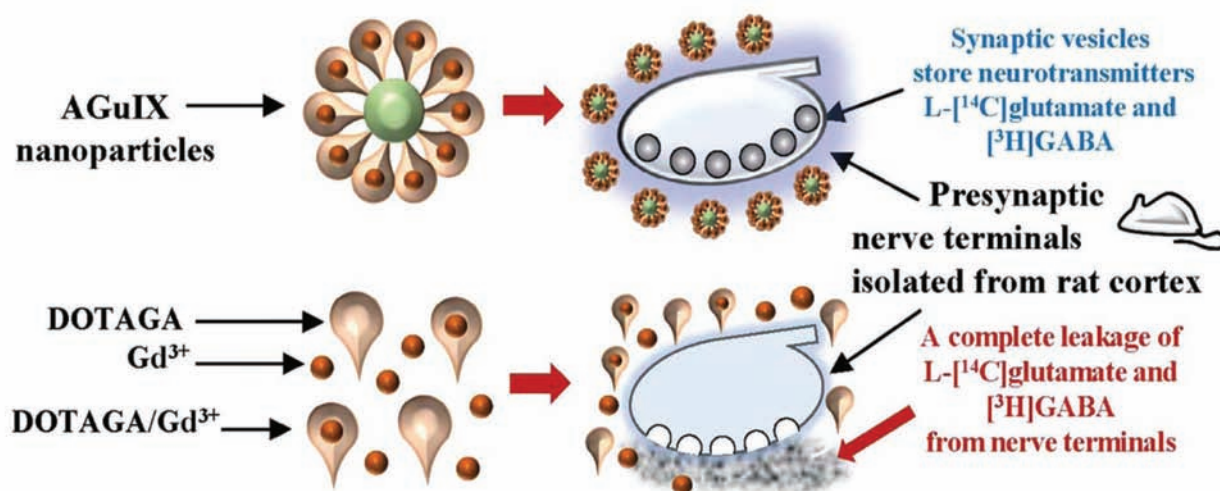


Fig. 4. Design of experiments to study the effect of gadolinium-containing nanohybrids on synaptic transmission [50]

Modulation of synaptic neurotransmission was performed using simultaneous depletion of cholesterol in the plasma membrane of nerve terminals and hypothermia. An additive neuroprotective effect was shown with the combined action of cholesterol depletion in the membrane of nerve terminals and hypothermia, and cholesterol depletion cannot normalize hypothermia-induced changes in the lipid order of the plasma membrane of nerve terminals [51].

The mechanism of action of the antiviral drug remdesivir has been proven. It has been shown for the first time that remdesivir was able to increase the conductance of the planar bilayer membrane by forming stable voltage-dependent non-ion-selective pores. It has been shown that remdesivir reduced the release of neurotransmitters by exocytosis. Remdesivir did not provoke the development of excitotoxicity and did not change the passive permeability of the membrane for neurotransmitters. However, a decrease in the extracellular level of [³H]GABA under the action of remdesivir may weaken synaptic inhibition and change the balance of excitatory and inhibitory signals. Our data indicate that the dosage of remdesivir during antiviral therapy should be precisely controlled to prevent a possible neuromodulatory effect at the presynaptic level [52].

It has been shown that the complexation of human serum albumin with quercetin occurred with a change in the secondary structure of the protein due to a change in the hydrophobic local environment near the amino acid residue Trp214, which is impor-

tant for the creation of self-assembled nanostructures in biotechnology [53].

Attention is also paid to the study of gut-brain communication, which is the most promising modern research for indirect correction of neurological disorders [34, 54].

Scientific and educational activity among students is led by V. I. Nazarenko. It concerned ways and methods of scientific and educational activity of the Institute in cooperation with the Extracurricular Educational Institution "Junior Academy of Sciences of Ukraine". This activity rooted back to the time of Oleksandr Volodymyrovych Palladin's work, and currently continues in collaboration with the Youth Section of the Ukrainian Biochemical Society [55].

In 2025, the Department received a grant for its research within the framework of the Horizon Europe Programme.

The results of the Department's research create a neurochemical basis and open ways to overcome neurological disorders. There is considerable interest worldwide in solving the problem of controlling neuronal activity, preventing and diagnosing neuropathologies, and identifying trigger factors for the development of neurodegenerative diseases. Since such advanced technologies do not yet exist, these findings can be implemented not only in Ukraine, but also in other countries and can have a significant economic contribution to the sustainable development of the State.

Conflict of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ВІДДІЛ НЕЙРОХІМІЇ З 1925 РОКУ ДО НАШИХ ДНІВ

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Описано діяльність відділу нейрохімії з 1925 року до сьогодні. Основними науковими напрямками досліджень відділу біохімії нервової системи до 1982 року були: вивчення хімічної топографії нервової системи; вивчення субклітинної та суборганної локалізації нейроспецифічних протеїнів; дослідження впливу психотропних речовин на метаболізм азоту, вуглеводів та протеїнів у структурах нервової системи; вивчення мембранної організації та механізмів функціонування ензимних систем активного транспорту натрію, калію та кальцію в нервових клітинах. З 1982 року дослідження відділу зосереджені переважно на таких напрямках: біогенез мембранних та секреторних протеїнів; дослідження нейроспецифічних протеїнів; дослідження плазматичних мембран, що безпосередньо беруть участь у генерації та передачі нервових сигналів. З 2010 року дослідження відділу нейрохімії спрямовані на вирішення наступних актуальних проблем: з'ясування ролі структурної організації мембрани та ліпід-протеїнових взаємодій у регулюванні процесу передачі нервових сигналів; з'ясування ролі пресинаптичних рецепторів у регулюванні ключових етапів процесу нейротрансмісії та визначення шляхів модулювання системи рецепції нейромедіаторів; пошук та ідентифікація природних мембранотропних та нейроактивних сполук; аналіз молекулярних механізмів дії мембранотропних та

нейроактивних препаратів; космічна біологія, а саме розробка методу визначення токсичності планетарного пилу; нанотехнології, а саме синтез та аналіз нейроактивного ефекту наночастинок; екологічна нейротоксикологія, а саме вивчення нейротоксичної дії забруднювачів навколишнього середовища та розробка шляхів подолання їх шкідливого впливу.

Ключові слова: синаптична нейротрансмісія, нервові терміналі, екзоцитоз, транспортери нейромедіаторів, рецептори, мембранотропні та нейроактивні сполуки, функціональні нанокompозити та наногібриди.

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