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REVIEWS

Evolution of Cell-to-Cell Communication and the Structural Brain Organization

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Abstract—The review considers key issues of historical development of the nervous system, including evolution of the brain intercellular contacts and neurotransmitter systems. Special attention is given to the structural-functional organization of the central nervous system in a freshwater pulmonate gastropod, *Lymnaea stagnalis*.

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The nervous system, in the course of its historical development, has passed pathway from a small-numbered population of primitive sensory cells located within the limits of body integuments (ectoderm) to multimillion and multibillion associations of neuronal and accessory (glial) elements arranged in an apparatus of management of the work of the whole organism.

EVOLUTION OF THE NERVOUS SYSTEM AND LOCALIZATION OF FUNCTIONS

The least advanced organization is characteristic of the *network-like* or *diffuse* nervous system of coelenterates [1, 2]. In this case the neuronal processes are dispersedly distributed in the ectoderm, form synaptic contacts and involve the entire animal body was a network. Such a structure is traditionally considered to be unable to provide differentiated reaction to stimulation, as the rapid (up to 120 cm/s) transduction of excitation from a stimulated point in all directions involves the *entire* organism in the response reaction. This statement is to be taken with a grain of salt. Thus, in the freshwater hydra, there have been found several stereotypic alimentary, locomotor, and defensive reactions accompanied by coordinated movements of various parts of the body [3]. Besides, this animal group shows obvious signs of centralization, i.e., concentration of neurons in certain body areas, such as the basal disc and oral neuronal clusters in hydra and rhopalia in jellyfish [4, 5].

In the course of further development of the nervous system, the number of its constituent structures rise, which provides reliable ground for management of the increasing number of motor reactions. This occurs on the background of formation of cell clusters of their composing elements. As a result, the appearance of separate neuronal masses indicates transition to the nervous system of the *ganglion* type [1—3].

Intraganglionic consolidation of neurons connected to each other as well as to receptors and effector organs has provided reliable interactions between separated alimentary, respiratory, circulatory, reproductive, motor, and other systems. The parallel increase of the central nervous structures that are in the subordinate dependence on

each other makes it possible the coordinated functioning of the above-mentioned organism systems. Various subtypes of the ganglionic nervous system (the *diffuse-ganglionic* in molluscs, the *ladder* type and the *chain* type in worms and arthropods) are variants of one initial basic scheme implying agglomeration of neurocytes near their controlled body region 6]. Such segmentary organization allows only a part of nerve cells to be involved in a response reaction and thereby increases the ability of the nervous system to process signals received through different sensory inputs. Further complication of this nervous system is accompanied by enlargement of its size, a shortening of interganglionic fibers (the connectives between ganglia also lose their cells), approaching and fusion individual ganglia into more massive brain conglomerates [7, p. 71] located as a rule in the anterior part of the body (the head). The solid nerve strand represented by the *tubular* system of chordates, with its segmentary structure in the truncal region (the spinal cord) and a thickening of the anterior part (the brain), has certain features of similarity with the considered variant of the final evolution of the chain type systems.

Logically, ganglionic organization of the nervous tissue would have resulted in concentration of the neurons belonging to *the same* functional network within a single ganglion, and in coordinational interactions between ganglia, i.e., different functional systems. But the actual situation is far away from the above-exposed one. For instance, in the mollusc *Lymnaea stagnalis*, respiratory network neurons are located at least in three ganglia: the right pedal, right parietal, and visceral [8, 9]; those of alimentary network, in four: the left and right buccal and the cerebral [10, 11]; protective cells have been identified in the visceral, both pedal, and both parietal ganglia [12, 13]; locomotor neurons, in pedal ganglia [14, 15], etc. Some ganglia are characterized by the higher autonomy, e.g., buccal ones and osphradium. Therefore, neurons sharing the same functional role are not strictly confined to a single ganglion, which is shown both by the above data and by results of analysis of cellular bases of behavior and regulation of physiological functions in neuroscience model organisms [7]. At best, one can be stated that nerve cells of a given functional network are *primarily* located in a certain ganglion.

The neural network organization in the higher vertebrates has some features making it similar to that of invertebrate organisms. They include high autonomy and compactness of cell distribution in ganglia of the autonomic nervous system in a combination with the presence of dispersed elements in the cortical parts of analyzers [16]. I.P. Pavlov's concept of "dynamic localization of functions in the cerebral cortex" also emphasizes "erosion" of the neuronal network throughout the space occupied by the nervous tissue. Data on neocortex cytoarchitecture and systemic organization obtained by different research groups [17–22] completely confirm this idea. Virtually every brain tomography performed during task performance or under stimulation shows that increased activity is common to *several* brain areas [23, pp. 486–521] containing numerous cells.

EVOLUTION OF INTERNEURONAL CONTACTS

The progressing increase of the nerve cell number accompanied by formation of new synaptic junctions is an integral feature of evolution of the nervous system. Since synapses represent the key element in neural integration [24], it is their adequate development which underlies phylogenesis of the nervous tissue.

Presumably, the initial pathway of signaling from cell to cell served cytoplasmic bridges between neurons in the composition of syncytium. These structures are present in the brain both early in ontogenesis [25] and in adults individuals [26]. Somewhat different by morphology, but functionally similar to contacts of the syncytial type are electrotonic synapses. Cytoplasmic interconnections between adjacent cells by means of protein cylinders (connexins/innexins) allow unhindered cell-to-cell exchange of molecules [27]. The wide spreading of gap junctions in animals located at different steps of evolution and in the vast majority of cell populations from tissues of animal organisms [28] also indicates the ancient origin of these contacts.

Until the present time it still remains poorly understood how connexins from adjacent cells become so finely "tuned" to each other that even the

ion leakage from the connexon region into the intercellular space is made impossible. Probably, this is a consequence of the previously existing syncytial contacts between cells, which allowed coordination of intracellular translocation of structural molecules, including connexins, but then disappeared after creation of the fully functioning gap junction; selectivity of this contact became much higher than that of a simple cytoplasmic bridge due to a conformational rearrangement of its pore diameter.

In spite of the obvious complexity of the subcellular machinery responsible for chemical synapse proper functioning, as compared with other types of communication contacts, these junctions are not evolutionarily recent. Even in the simplest representatives of coelenterates the presence of true chemical synapses between neurons has been shown; moreover, they are always formed by neurons of different types [29].

As follows from the above data, there are no strict proofs of evolutionary precedence of electrotonic synapses over the chemical ones. Apparently, they emerged in parallel with the only difference that gap junctions were aimed only toward intercellular communication within the same tissue, whereas chemical synapses—also toward interactions of cells of different tissue (neuromuscular and neuroglandular junctions). Contacts of the latter type provide information transduction over distances many times preceding the size of the single cell. It is to be noted that electrochemical junctions identified by neurophysiologists represent chemical synapses with several morphological peculiarities, i.e., the larger synaptic contact area and the presence of numerous glial elements densely surrounding the synaptic region [24, 30].

It was suggested that in the course of evolution the ratio of electrical and chemical synapses decreased progressively in favor of the latter [31, 32]. It is considered that «the more complexly organized chemical synapses provide so much higher specificity and adjustability of intercellular communication that they considerably displaced the electrical ones» (cited after [33], p. 67). This statement needs several elucidations.

Indeed, the adjustability of chemical synapses is very high, but gap junctions also can be modified under the effect of various extracellular (neurotransmitters) and intracellular (cyclic nucleotides) factors [28, 34]. Chemical junctions are sensitive to low temperatures [35, 36], while the electric ones, by contrast, are heat-sensitive [37, 38], which may explain their lower representation in homoiotherms. It is admitted, however, that temperature cannot be considered the major factor determining use of some particular mechanism [32]. On the other hand, electrotonic synapses are not submitted to fatigue and synaptic depression, are resistant to action of various neurotoxins and do not have synaptic delay in signal transmission. At the same time, cell differentiation requires the complete uncoupling of the cytoplasm of interacting cells and, as a consequence, destruction of contacts of the gap junction-type—the number of electrical synapses decreases in the course of embryogenesis [39].

However, the main "disadvantage" of the electrotonic contact is considered to be *impossibility of performing inhibition* at development of excitation in the presynaptic cell, which considerably reduces *functional* capabilities of these contacts, Actually, this means the absence of any coordination interactions between structural elements of nerve centers (for instance, the reciprocal and recurrent inhibition) and between the centers themselves. It becomes impossible to provide consecutive connection of neurons of different types. As a sequence, the gap junctions within the limits of the nervous system are present in the parts where synchronization of electrical activity within groups of cells is needed, i.e., they provide parallel arrangement of functionally similar adjacent neurons [32, 40].

Thus, in the central nervous system of the mollusc *Lymnaea stagnalis*, electrotonic synapses are found between neurons of the alimentary [10], locomotor [15], and respiratory [41] networks of defensive, modulator, and neurosecretory cells [42, 43] from the predominant majority of ganglia. There is no experimental evidence for their existence between interneurons belonging to *different* neural networks, e.g, of the alimentary and respiratory ones.

Thus, chemical junctions using various neurotransmitter substances as signaling molecules are the necessary component of coordination interactions between nervous centers.

EVOLUTION OF CHEMICAL SIGNAL TRANSDUCTION

From the chemical point of view, the whole diversity of neurotransmitters and neuromodulators, in I.P. Ashmarin's opinion [44], can be divided into two large groups: monomolecular and polymeric. The first group includes amino acids (glycine, glutamic acid, aspartic acid, GABA), their derivatives (dopamine, noradrenaline, adrenaline, serotonin, histamine), acetylcholine, ATP and its derivatives, and volatile molecules (NO, CO), the second group—numerous neuropeptides (neurokinins, opioid peptides, substance P, etc.).

It has turned out that there are no data indicating scarcity of the transmitter set in animals with the simply organized nervous system [6, 45]. Even coelenterates, for instance, hydra, are characterized by the presence in the nervous system of several neurotransmitters—dopamine [46] and GABA [47]. Representatives of the group of monomolecular neurotransmitters (neuromodulators) are not to be considered as initial signaling substances. The appearance of compound of the non-peptide nature often represents the more complex process than a slight change in the primary structure of a short portion of the polypeptide chain [44]. Actually, this needs the presence of novel enzymatic systems and of the corresponding genes. The neoformation of peptide mediators can be provided by usual of mutagenesis, while subsequent translation of the novel gene product can occur with participation of the already available protein assembles. A reflection of such processes is formation of the majority of active neuropeptides from the large molecule-precursor, i.e., they represent product of one gene [48].

The wide spreading of regulatory peptides in organisms with the simply organized nervous system [6, 46. 49, 50] also indicates evolutionary antiquity of this group compounds. On the other hand, monomolecular neurotransmitters, such as amino acids and/or ATP, are also present in animals located at initial steps of evolutionary ladder and by no means in occasional cases [3, 46]. Perfection of ways of action of signal molecules is connected with the appearance of novel enzymatic systems [44, 45] responsible for removal of excess of transmitter from the extracellular space (the synaptic gap) and restriction of the area of its action.

From the point of view of efficiency of use of chemical model as a mediator of interaction between cells, it is impossible to give preference to some group of substances. It can only be stated about the *quantitative* predominance of some type of transmitters over others in different groups of animals. Thus, in the course of phylogenesis, the portion of the peptidergic and monoaminergic neurons is restricted with a rise of the number of cells synthesizing the low molecular compounds of the type of acetylcholine and amino acids [45]. Formation of new monomolecular neurotransmitters highly specific from the viewpoint of synthesis and subsequent inactivation of monomolecular neurotransmitters opens possibilities to provide regulatory actions in the newly appearing combinations of neurons (neuronal networks).

At present, the reason why there are so many neurotransmitters in separate nerve networks within the nervous system, even at the simplest levels of its organization, still remain unclear. The primary function of each signaling molecule evidently consists in excitation or inhibition of activity of the target cell. This can be achieved with only two or even *one* neurotransmitter throughout the entire central nervous system. A presynaptic neuron (i.e., the structure utilizing the single neurotransmitter) potentially can exert opposite effects, both exciting and inhibiting, on different postsynaptic cells which was shown for the first time in the mid-1960s in the nervous system of Aplysia [51, 52].

The above question can be answered with the hypothesis of the *nervous tissue polygenesis* (D.A. Sechenov, 1974). According to his hypothesis, multiple and independent origins of neurons from different cell lineages, each with its own transmitters, are proposed [50]. One of the proofs in favor of this hypothesis is the fact of neuronal specificity even in most primitive organisms: serotonin-containing cells differ in their locations and connections from those using another transmitter, e.g., dopamine [53, 54]. In other words, nerve cells belonging to a certain network use predominantly some particular *certain* neurotransmitter. This is what allows affecting *individual* functions controlled by the nervous system.

In the early 1990s, the concept was put forward

that every neurotransmitter secreted by a cell, apart from the signaling function within the synapse, also provides a possibility for integration of local network elements [55, 56]. As a result, the target of a neurotransmitter is the network as a whole, and responses of its elements to the applied transmitter are mutually coordinated [57, 58]. Actually, it is the multiplicity of signaling compounds used in the intercellular communication which is the ground both for coordination interactions between the nerve network cells and for interactions between networks. Formation of *transmitter-dependent behavior*, i.e., establishment of a novel coordinate state of the organism, has been shown in a huge number of species—from various groups of invertebrate organisms to the higher vertebrates. It is obvious to be founded on *unequal sensitivity* of neurons to action of some particular chemical regulator, which is provided by diversity of receptor structures.

In particular, the neurotransmitter representation of neuronal networks of mollusc *Lymnaea stagnalis* is rather rich [59]. The *leading role* in coordinate activity of each cellular ensemble belongs to only one of a variety of possible signaling molecules. Thus, functioning of the central respiratory rhythm generator requires necessarily dopamine [60, 61], the locomotor one—serotonin [62], and the alimentary one—glutamate and/or nitric oxide [63, 64]. All this does not mean that other neurotransmitters do not have a modulating effect on the mentioned behavioral patterns. Thus, pulmonary respiration in *Lymnaea stagnalis* is submitted to effect of adrenaline/noradrenaline and GABA [60], serotonin [65], and nitric oxide [66]. The food-procuring activity is adjusted with participation of opioid peptides, serotonin [67, 68], and other signaling molecules [69].

Genetic studies (the transcriptome analysis) of neurons of Aplysia also have revealed the widest representation of different receptors in individual cells [70]. This fact proves indirectly that every element of the network is ready for perception of numerous regulatory actions. The resultant reaction of the network is determined by location of receptors, rather than of the source of synthesis of some particular transmitter [56]. On the other hand, peculiarity of any input from an afferent and/or command neuron is strong dependence of the network neuronal responses on a certain chemical signal.

CONCLUSION

Thus, owing to the presence of numerous signaling molecules used in the central nervous system as neurotransmitters and/or neuromodulators, there is provided a possibility of effective coordination of activity of nervous centers. Actually, this allows individual cells to be involved in functionally different neuronal networks, i.e., indicates the constant *dynamic* character of interconnection of the brain nervous structures. Establishment of new interneuronal combinations, in turn, allows achieving the optimal resultant activity of the organism functional systems, which is directed at formation of the motor response providing the adaptive result required under the current conditions.

REFERENCES

1. *Biologicheskii entsiklopedicheskii slovar'* (Biological Encyclopedical Dictionary), Gilyarov, M.S., Ed., Moscow, 1989.
2. *Evolyutsionnaya fiziologiya* (Evolutionary Physiology), Handbook on Physiology in 2 vol., vol. 1, Leningrad, 1979.
3. Lapitskii, V.P., *Sravnitel'naya fiziologiya nervnoi sistemy* (Comparative Physiology of the Nervous System). St. Petersburg, 2004.
4. Beklemishev, V.N., *Osnovy sravnitel'noi anatomii bespozvonochnykh* (Grounds of Comparative Anatomy of Invertebrates), vol. 2, Moscow, 1964.
5. Dogel, V.A., *Zoologiya bespozvonochnykh* (Invertebrate Zoology), Moscow, 1981.
6. Prosser, K.L., *Tsentral'naya nervnaya sistema* (Central Nervous System), Comparative Animal Physiology, vol. 3, Prosser, K.L., Ed., Moscow, 1978, pp. 5–163.
7. Kandel, E.R., *Kletochnye osnovy povedeniya* (Cellular Grounds of Behavior), Moscow, 1980.
8. Syed, N.I., Harrison, D., and Winlow, W., Respiratory Behavior in the Pond Snail *Lymnaea stagnalis*. I. Behavioral Analyses and the Identification of Motor Neurones, *J. Comp. Physiol.*, 1991, vol. 169A, pp. 541–555.
9. Syed, N.I. and Winlow, W., Respiratory Behavior in the Pond Snail *Lymnaea stagnalis*. II. Neural Elements of the Central Pattern Generator (CPG), *J. Comp. Physiol.*, 1991, vol. 169A, pp. 557–568.
10. Benjamin, P.R., Staras, K., and Kemenes, G., A

Systems Approach to the Cellular Analysis of Associative Learning in the Pond Snail Lymnaea, *Learning and Memory*, 2000, vol. 7, pp. 124–131.
11. McCrohan, C.R. and Benjamin, P.R., Patterns of Activity and Axonal Projections of the Cerebral Giant Cells of the Snail *Lymnaea stagnalis*, *J. Exp. Biol.*, 1980, vol. 85, pp. 149–168.
12. Moroz, L.L. and Winlow, W., An Identified, Multifunctional, Giant Neurone of the Left Parietal Ganglion is Involved in Control of Defensive Behaviour in Lymnaea, *J. Physiol.*, 1990, vol. 435, p. 117P.
13. Sakharov, D.A., Integration of High Threshold Whole-Body Withdrawal in the Pond Snail, *Signal Molecules and Behaviour*, Winlow, W., Vinogradova, O.V., and Sakharov, D.A., Manchester: Manchester Univ., 1991, pp. 124–130.
14. Tsyganov, V.V., Coordination of Activity of Monoaminergic Pedal Neurons in Freshwater Snails, *Ross. Fiziol. Zh. im. I. M. Sechenova*, 2000, vol. 86, pp. 369–378.
15. Syed, N.I. and Winlow, W., Morphology and Electrophysiology of Neurons Innervating the Ciliated Locomotor Epithelium in *Lymnaea stagnalis* (L.), *Comp. Biochem. Physiol.*, 1988, vol. 93A, pp. 633–644.
16. Borzyak, E.I., Bocharov, V.Ya., and Sapin, M.R., *Anatomiya cheloveka* (Human Anatomy) in 2 vol., vol. 2, Moscow, 1993.
17. Adrianov, O.S., *O printsipakh organizatsii integrativnoi deyatel'nosti mozga* (About Principles of Organization of the Brain Integrative Activity), Moscow, 1976.
18. Batuev, A.S., *Vysshie integrativnye sistemy mozga* (Higher Integrative Systems of the Brain), Leningrad, 1981.
19. Livanov, M.N., *Prostranstvennaya organizatsiya protsessov mozga* (Spatial Organization of the brain processes), Moscow, 1972.
20. Mountcastle, V., The Organizing Principle for Brain Function—the Elementary Module and the Distributed System, *The Intelligent Brain*, Edelman, G.M. and Mountcastle, B., Eds., Moscow: Mir, 1981, pp. 15–67.
21. Simonov, P.V., *Emotsional'nyi mozg* (The Emotional Brain), Moscow, 1981.
22. Hubel, D.H. and Wiesel, T.N., Functional Architecture of Macaque Monkey Visual Cortex (Ferrier Lecture), *Proc. R. Soc. Lond. B*, 1977, vol. 198, pp. 1–59.
23. Nicholls, J.G., Martin, A.R., Wallace, B.G., and Fuchs, P.A., *Ot neirona k mozgu* (From Neuron to Brain), Moscow, 2003.
24. Eccles, J.C., Fiziologiya sinapsov (Physiology of Synapses), Moscow, 1966.
25. Sotnikov, O.S., Malashko, V.V., and Rybakova, G.I., Syncytial Connection of Neurons in Tissue Culture and Early Ontogenesis, *Morfologiya,* 2007, vol. 131, pp. 7–15.
26. Sotnikov, O.S., Paramonova, N.M., and Archakova, L.I., Interneuronal Cytoplasmic Syncytial Connections in Hippocampus, *Novosti Med.-Biol. Nauk*, 2008, vols. 1–2, pp. 62–67.
27. Bruzzone, R. and Ressot, C., Connexins, Gap Junctions and Cell–Cell Signalling in the Nervous System, *Eur. J. Neurosci.*, 1997, vol. 9, pp. 1–6.
28. Saez, J.C., Berthoud, V.M., Branes, M.C., Martinez, A.D., and Beyer, E.C., Plasma Membrane Channels Formed by Connexins: Their Regulation and Functions, *Physiol. Rev.*, 2003, vol. 83, pp. 1359–1400.
29. Westfall, J.A., Synapses in a Primitive Coelenterate, *J. Cell Biol.*, 1971, vol. 51, pp. 318–323.
30. Martin, A.R. and Pilar, G., Dual Mode of Synaptic Transmission in the Avian Ciliary Ganglion, *J. Physiol.*, 1963, vol. 168, pp. 443–463.
31. Shapovalov, A.I., Interneuronal Synapses with Electrical and Chemical Mechanisms of Transmission and Evolution of the Central Nervous System, *Zh. Evol. Biokhim. Fiziol.,* 1977, vol. 13, pp. 621–632.
32. Shapovalov, A.I., Evolution of Mechanisms of Connection between Neurons: Electrical, Mixed, and Chemical Synapses, *Zh. Evol. Biokhim. Fiziol.*, 1979, vol. 15, pp. 268–277.
33. Dudel, J., Intercellular Transmission of Excitation, *Fiziol. Chelov. in 3 vol.*, vol. 1, Moscow, 1996, pp. 51–68.
34. Wildering, W.C., Synaptic Plasticity in the Adult Pond Snail *Lymnaea stagnalis*, Ph.D. Dissertation, Enschede: Febodruk BV, 1992, 170 pp.
35. Katz, B. and Miledi, R., The Effect of Temperature on the Synaptic Delay at the Neuromuscular Junction, *J. Physiol.*, 1965, vol. 181, pp. 656–670.
36. Sidorov, A.V., Effect of Temperature on Synaptic Transmission between Identified Neurones of the Mollusc *Lymnaea stagnalis*, *Neurosci. Lett.*, 2002, vol. 333, pp. 1–4.
37. Heitler, W.J. and Edwards, D.H., Effect of Temperature on a Voltage-Sensitive Electrical Synapse in Crayfish, *J. Exp. Biol.*, 1998, vol. 201, pp. 503–513.
38. Sidorov, A.V. and Kazakevich, V.B., Electrical Coupling between Identified Lymnaea Neurons: Nitric Monoxide and Temperature Action, *Protein Modules in Cellular Signalling*, Heilmeyer, L. and Friedrich, P., Eds., NATO Science Series: Life Sciences, 2001, vol. 318, pp. 150–153.
39. Bennett, M.M.L., Spray, D.C., and Harris, A.L.,

Electrical Coupling in Development, *Amer. Zool.*, 1981, vol. 21, pp. 413–427.
40. Berry, M.S. and Pentreath, V.W., The Integrative Properties of Electrotonic Synapses, *Comp. Biochem. Physiol.*, 1977, vol. 57A, pp. 289–295.
41. Benjamin, P.R. and Pilkington, J.B., The Electrotonic Location of Low-Resistance Intercellular Junctions between a Pair of Giant Neurones in the Snail Lymnaea, *J. Physiol.*, 1986, vol. 370, pp. 111–126.
42. Benjamin, P., Electrical Properties of the Dark Green Cells, Neurosecretory Neurones in the Brain of the Pond Snail, *Lymnaea stagnalis*, *Comp. Biochem. Physiol.*, 1983, vol. 75A, pp. 549–559.
43. Benjamin, P. and Winlow, W., The Distribution of Three Wide-Acting Synaptic Inputs to Identified Neurones in the Isolated Brain of *Lymnaea stagnalis* (L.), *Comp. Biochem. Physiol.*, 1981, vol. 70A, pp. 293–307.
44. Ashmarin, I.P., Neuromediators and Neuromodulators. Evolution of Compounds and Evolution of Theories, *Zh. Evol. Biokhim. Fiziol.*, 1979, vol. 15, pp. 278–282.
45. Kostyuk, P.G., The Main Nerve Processes as a Fundament for Evolution of Nervous Activity, *Zh. Evol. Biokhim. Fiziol.*, 1979, vol. 15, pp. 222–226.
46. Kass-Simon, G. and Pierobon, P., Cnidarian Chemical Neurotransmission, an Updated Overview, *Comp. Biochem. Physiol. A. Mol. Integr. Physiol.*, 2007, vol. 146, pp. 9–25.
47. Pierobon, P., Concas, A., Santoro, G., Marino, G., Minei, R., Pannaccione, A., Mostallino, M.C., and Biggio, G., Biochemical and Functional Identification of GABA Receptors in *Hydra vulgaris*, *Life Sci.*, 1995, vol. 56, pp. 1485–1497.
48. Darlison, M.G. and Richter, D., Multiple Genes for Neuropeptides and Their Receptors: Co-Evolution and Physiology, *Trends Neurosci.*, 1999, vol. 22, pp. 81–88.
49. Nauta, W. and Feiertag, M., Organization of the Brain, *Brain,* Moscow: Mir, 1982.
50. Sechenov, D.A., *Genealogiya neironov* (Genealogy of Neurons), Moscow, 1974.
51. Kandel, E.R., Frazier, W.T., Waziri, R., and Coggeshall, R.E., Direct and Common Connections among Identified Neurons in Aplysia, *J. Neurophysiol.*, 1967, vol. 30, pp. 1352–1376.
52. Wachtel, H. and Kandel, E.R., A Direct Synaptic Connection Mediating both Excitation and Inhibition, *Science,* 1967, vol. 158, pp. 1206–1208.
53. Cottrell, G.A., Abernethy, K.B., and Barrand, M.A., Large Amine-Containing Neurons in the Central Ganglia of *Lymnaea stagnalis*, *Neurosci.,* 1979, vol. 4, pp. 685–689.
54. Winlow, W., Haydon, P.G., and Benjamin, P.R., Multiple Postsynaptic Actions of the Giant Dopamine-Containing Neuron R.Pe.D.1 of *Lymnaea stagnalis*, *J. Exp. Biol.*, 1981, vol. 94, pp. 137–148.
55. Sakharov, D.A., The multiplicity of neurotransmitters: the functional significance, *Zh. Evol. Biokhim. Fiziol.*, 1990, vol. 26, pp. 733–741.
56. Sechenov, D.A., Integrative Function of Serotonin in Primitive Metazoa, *Zh. Obshch. Biol.*, 1990, vol. 51, pp. 437–449.
57. Vorontsov, D.D., Tsyganov, V.V., and Sechenov, D.A., Central Mechanisms that Control Respiration in the Pulmonate Snail *Lymnaea stagnalis*: Phasic Coupling of Lung Ventilation to Cyclic Locomotion, *Dokl. RAN*, 2003, vol. 391, pp. 407–409.
58. Dyakonova, B.E. and Sechenov, D.A., The Neurotransmitter Ground for Mollusk Behavior: Regulation of Choice between Exploratory and Defensive Responses to an Unknown Object, *Zh. Vyssh. Nerv. Deyat. im. I.P. Pavlova*, 1994, vol. 44. pp. 526–531.
59. S.-Rosza, K., The Pharmacology of Molluscan Neurons, *Prog. Neurobiol.*, 1984, vol. 23, pp. 79–150.
60. Moroz, L.L., Monoaminergic Mechanisms of Respiratory Behavior in Pulmonate Freshwater Mollusks: Pharmacological and Cellular Analyses, *Candidate Sci. Dissertation*, Moscow, 1988.
61. Syed, N.I., Bulloch, A.G.M., and Lukowiak, K., *In vitro* Reconstruction of the Respiratory Central Pattern Generator of the Mollusk Lymnaea, *Science,* 1990, vol. 250, pp. 282–285.
62. Tsyganov, V.V. and Sechenov, D.A., Locomotor Rhythms in the Pond Snail *Lymnaea stagnalis*: Site of Origin and Neurotransmitter Requirements, *Acta Biol. Hung.*, 2000, vol. 51, pp. 189–195.
63. Brierley, M.J., Staras, K., and Benjamin, P.R., Behavioral Function of Glutamatergic Interneurons in the Feeding System of Lymnaea: Plateauing Properties and Synaptic Connections with Motor Neurons, *J. Neurophysiol.*, 1997, vol. 78, pp. 3386–3395.
64. Moroz, L.L., Park, J.H., and Winlow, W., Nitric-Oxide Activates Buccal Motor Patterns in *Lymnaea stagnalis*, *Neuroreport,* 1993, vol. 4, pp. 643–646.
65. Tsyganov, V.V., Neuronal Correlates of Serotonin-Dependent Motor Behavior in the Pond Snail *Lymnaea stagnalis*, *Candidate Sci. Dissertation*, Moscow, 2001.
66. Sidorov, A.V. and Maslova, G.T., The State of Antioxidative Protection in Central Nervous Ganglia of Mollusc *Lymnaea stagnalis* at Modulation

of Activity of the NO-Ergic System, *Zh. Evol. Biokhim. Fiziol.*, 2008, vol. 44, pp. 453–458.
67. Dyakonova, V.E. and Sechenov, D.A., Participation of the Endogenous Opioid System in Regulation of the Alimentary and Protective Behaviors of Mollusk *Lymnaea stagnalis*, *Zh. Vyssh. Nerv. Deyat. im. I.P. Pavlova,* 1994, vol. 44, pp. 316–322.
68. Yeoman, M.S., Pieneman, A.W., Ferguson, G.P., Ter Maat, A., and Benjamin, P.R., Modulatory Role for the Serotonergic Cerebral Giant Cells in the Feeding System of the Snail Lymnaea. I. Fine Wire Recording in the Intact Animal and Pharmacology, *J. Neurophysiol.*, 1994, vol. 72, pp. 1357–1371.
69. Elliott, C.J.H. and Susswein, A.J., Comparative Neuroethology of Feeding Control in Molluscs, *J. Exp. Biol.*, 2002, vol. 205, pp. 877–896.
70. Moroz, L.L., Edwards, J.R., Puthanveettil, S.V., Kohn, A.B., Ha, T., Heyland, A., Knudsen, B., Sahni, A., Yu, F., Liu, L., Jezzini, S., Lovell, P., Iannucculli, W., Chen, M., Nguyen, T., Sheng, H., Shaw, R., Kalachikov, S., Panchin, Y.V., Farmerie, W., Russo, J.J., Ju, J., and Kandel, E.R., Neuronal Transcriptome of Aplysia: Neuronal Compartments and Circuitry, *Cell*, 2006, vol. 127, pp. 1453–1467.