## Head of Laboratory

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## Lab members

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**Area of research:**

1. Investigation of the mechanisms of non-quantum acetylcholine release
2. Investigation of the mechanisms of action of a new class of inhibitors of acetylcholine esterase
3. Investigation of the role of the kinetics of the neurotransmitter secretion in the reliability of synaptic transmission
4. Research of the molecular mechanisms of regulation of endogenous neurotransmitter release from the nerve terminals
5. Investigation of mechanisms of the blocking receptor-channel complex of postsynaptic membrane

**Main results of studies:**

1. It was found that the release of neurotransmitter from synaptic vesicles is accompanied by the formation of the “directed” micro-flow which could enhance the efficiency of neurotransmitter action on receptors of the target cell, ensuring the reliability of synaptic excitation.

2. It was shown that magnesium ions could reduce the intensity of non-quantal neurotransmitter release. It was proved that extracellular calcium was necessary to implement non-quantal release of neurotransmitter, but the participation of extracellular calcium ions in the process of non-quantal secretion was not direct and was not mediated by their entry via calcium channels, as in the case with quantal secretion. At the same time, the sensitivity of non-quantal mechanism of neurotransmitter release to magnesium ions was specific and was not related to the ability of these ions to block calcium channels. (The results were included in the list of the main achievements of RAS in 2009).

3. The  mechanism of autoregulation of non-quantal release of acetylcholine was found in the neuromuscular synapse of mammalians activated by both main neurotransmitter acetylcholine and glutamate,  co-released in a free form from the nerve terminal as a co-mediator or formed by the hydrolysis of neuropeptide N-acetylaspartylglutamate in the synaptic cleft. (The results were included in the list of the main achievements of RAS in 2007.)

4. It was found that the inhibition of butyrylcholinesterase changed the amplitude and time parameters of postsynaptic responses after blockade of acetylcholinesterase, the main enzyme responsible for rapid hydrolysis of neurotransmitter, demonstrating that butyrylcholinesterase was localized in close proximity to release sites (These results were included in the list of the main achievements of RAS in 2009).

5. For the first time it was shown that, in contrast to classical acetylcholinesterase inhibitors, a new class of inhibitors of this enzyme, derivatives of 6-methyluracil, inactivated functional synaptic acetylcholinesterase more effectively in synapses of locomotor muscles compared to synapses of diaphragm muscle, pointing to the distinction of cholinesterase properties in synapses of muscles of different functional types. Screening of some compounds of this class according to ability to inhibit acetylcholinesterase in different organs revealed the reagents facilitating the synaptic transmission in neuromuscular junction at doses not causing any side-effects associated with acetylcholinesterase inactivation in heart and smooth muscles. This allows to consider these compounds as potential medical tools for treatment of myasthenia gravis and other syndromes of pathological muscle weakness.

6. The essential physiological role of the previously unexplored way of modulation of synaptic transmission by altering the kinetics of the release of quanta of neurotransmitter was proved. In some cases, this mechanism was the leading one in providing the reliable neuromuscular transmission, and the modulation of this mechanism could be important for overcoming the synaptic defects in certain types of pathology. (The results were included in the list of the main achievements of RAS in 2002.)

7. The leading role of calcium ions and cyclic AMP in the modulation of the kinetics of neurosecretion, particularly, the correlation between their intracellular level and the synchrony of the neurotransmitter release, was revealed.

8. When comparing the mechanisms of action of substances used in clinical practice (mecamylamine, chlorhexidine, demifosfon), it was established that these compounds were the blockers of cholinoceptive complexes with different mechanisms of action including the slow blocking of opened ion channels, the “trapping” block of the channel and allosteric modulation of the receptor-channel complex. On the basis of the experimental studies and mathematical modeling, the algorithm allowing to determine the mechanism of action of different modulators was developed.

**Selected Publications**

1. **Khuzakhmetova V, Samigullin D, Nurullin L, Vyskočil F, Nikolsky E, Bukharaeva E. Kinetics of neurotransmitter release in neuromuscular synapses of newborn and adult rats. Int J Dev Neurosci. 2014 Jan 9;34C:9-18.**

**2. Tsentsevitsky A, Kovyazina I, Nikolsky E, Bukharaeva E, Giniatullin R. Redox-sensitive synchronizing action of adenosine on transmitter release at the neuromuscular junction. Neuroscience. 2013 Sep 17;248:699-707.**

3. Petrov KA, Malomouzh AI, Kovyazina IV, Krejci E, Nikitashina AD, Proskurina SE, Zobov VV, Nikolsky EE. Regulation of acetylcholinesterase activity by nitric oxide in rat neuromuscular junction via N-methyl-d-aspartate receptor activation. Eur J Neurosci. 2013 Jan;37(2):181-189.

4. Shneider MN, Gimatdinov RS, Skorinkin AI, Kovyazina IV, Nikolsky EE.Hydrodynamic flow in a synaptic cleft during exocytosis. Eur Biophys J. 2012 Jan;41(1):73-78.

5. Abramochkin DV, Tapilina SV, Sukhova GS, Nikolsky EE, Nurullin LF. Functional M3 cholinoreceptors are present in pacemaker and working myocardium of murine heart. Pflugers Arch. 2012 Apr;463(4):523-52

6. Lindovský J, Petrov K, Krůšek J, Reznik VS, Nikolsky EE, Vyskocil F. Effect of tissue-specific acetylcholinesterase inhibitor C-547 on αβεδ and α3β4 acetylcholine receptors inCOScells. Eur J Pharmacol. 2012 Aug 5;688(1-3):22-26.

7. Malomouzh AI, Nurullin LF, Arkhipova SS, Nikolsky EE. NMDA receptors at the endplate of rat skeletal muscles: Precise postsynaptic localization. Muscle Nerve. 2011 Dec;44(6):987-989.

8. Malomouzh AI, Nikolsky EE, Vyskočil F. Purine P2Y receptors in ATP-mediated regulation of non-quantal acetylcholine release from motor nerve endings of rat diaphragm. Neurosci Res. 2011 Nov;71(3):219-225.

9. Tsentsevitsky A, Nikolsky E, Giniatullin R, Bukharaeva E. Opposite modulation of time course of quantal release in two parts of the same synapse by reactive oxygen species. Neuroscience. 2011 Aug 25;189:93-99.

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11. KA Petrov, Yagodina LO, GR Vale, Lannik NI Nikitashina AD, Rizvanov AA, VV teeth, Bukharaeva EA, VS Reznik, Nikolsky EE, Vyskočil F. Different sensitivities of rat skeletal muscles and brain Tues novel anti-cholinesterase agents, alkylammonium derivatives of 6-methyluracil (ADEMS). Br J Pharmacol. 20 11 Jun; 163 (4) :732-744th

12. Kovyazina IV, Tsentsevitsky AN, Nikolsky EE, Bukharaeva EA. Kinetics of acetylcholine quanta release at the neuromuscular junction during high-frequency nerve stimulation. Eur J Neurosci. 2010 Nov;32(9):1480-1489.

13. Shaihutdinova AR, Nikolsky EE, Vyskocil F, Skorinkin AI. Mechanisms of the inhibition of endplate acetylcholine receptors by antiseptic chlorhexidine (experiments and models). Naunyn

Schmiedebergs Arch Pharmacol. 2009 Dec;380(6):551-560.

14. Gilmanov IR, Samigullin DV, Vyskocil F, Nikolsky EE, Bukharaeva EA. Modeling of quantal neurotransmitter release kinetics in the presence of fixed and mobile calcium buffers. J. Computational Neuroscience , 2008, 25, 296-307.

15. Malomouzh A.I., Mukhtarov M.R., Nikolsky E.E., Vyskocil F. Muscarinic M1 acetylcholine receptors regulate the non-quantal release of acetylcholine in the rat neuromuscular junction via NO-dependent mechanism. J. Neurochemistry, 2007, 102, 2110-2117.

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