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The role of insulin receptor signaling in regulation of synaptic glutamatergic hippocampal neurotransmission

Proskura A.L.*, Vechkapova S.O., Ratushnyak A.S.
Federal Research Center of Information and Computational Technologies, Novosibirsk, Russia
** annleop@mail.ru*

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Motivation and Aim: The dendritic microprotrusions – dendritic spines – are the postsynaptic part of exciting synapses. Ionotropic glutamate receptors (NMDAR (The N-methyl-D-aspartate receptor), AMPAR (The α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) are key components of exciting synapses into a brain. Through structural proteins of postsynaptic density they form various protein macrocomplexes. It mediated of intermolecular rearrangements and form the functional regulatory networks [1]. In addition, the receptors of various hormones, in particular insulin, are present in the synaptic contacts zone.

Insulin is the most abundant peptidergic hormone secreted by the pancreatic islets of Langerhans and plays an important role in organic metabolism. The insulin receptor signaling in the brain have been various functions for normal neurophysiology, and a dysregulation of insulin secretion or insulin receptor signaling has been reported in serious mental illnesses [2]. Insulin has also been shown to regulate the endocytosis of synaptic AMPA receptors [3]. It is established that the activity of insulin receptors provides the maintenance of spine AMPAR density that probably mediates as basal neurotransmission as the long-term changens in the CA1 region of the hippocampus, at the same time the molecular mechanisms of these processes are described very superficially.

Results: The interactom of hippocampal dendritic spines was reconstructed (technology GeneNet was used (ROSPATENT No. 990006 от 15/02/1999)). The reception of the basic mediator signal – glutamat – is carried out by NMDAR macrocomplexes. A key event is the groundwork of second messengers pools. P4 → PIP2 (PtdIns(4,5)P2) catalyzated Phosphoinositide 5-kinase (PI5K), PIP2 → PIP3 (PtdIns(3,4,5)P3) mediated Phosphoinositide 3-kinase (PI3K). The AMPA subtype of glutamate receptors is subject to functionally distinct constitutive and regulated clathrin-dependent endocytosis, contributing to various forms of synaptic plasticity. It is established that insulin stimulated endocytosis of GluR2-AMPA receptors. This process has been accompanied disrupt interaction this subtype of receptors with synaptic scaffold proteins [3, 4].

To assess of insulin contribution to the processes of long-term potentiation induction, a series of experiments was carried out on hippocampal slices obtained from 2-month-old male ICR mice. Standard electrophysiological technique was used. Stimulation of Schaffer collaterals and recording of induced population spikes (p-spike) of pyramidal neurons in the CA1 field was performed via extracellular electrodes filled with physiological saline. A single stimulus inducing p-spike with amplitude ≤ 50 % of maximal amplitude was used for tetanization of the Schaffer collaterals. A stimulus of same intensity was used for analysis of responses after potentiation. Tetanization was induced by a single series of electric stimulation with a frequency of 100 Hz for 1 sec.

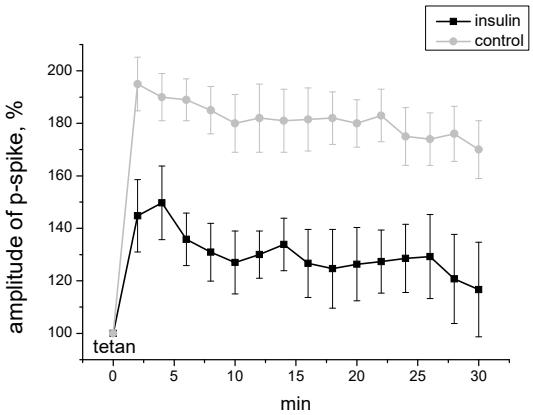

Fig. 1. Effects of insulin on long-term potentiation

Before tetanization, the slices were perfused with standard solution containing insulin (10 nM) for 30 min. The control slices were perfused the same time with the standard solution. 2 minutes after tetanization of the Schaffer collaterals, the amplitude of p-spike in the control group reached 195.5 ± 10.2 % of the basal level, while in the group incubated with insulin, it was significantly lower than in the control group, 144.8 ± 13.8 % of the basal level ($p \leq 0.01$). By the 30th minute after tetanization, the amplitude of p-spike in the control group reached 183 ± 9.5 %, and in the group incubated with insulin it was only 116 ± 15.1 % ($p \leq 0.001$). Insulin effects mediated of PIP3 accumulation, that provides the prolonged of PKC activity. PKC mediate GluR2-AMPAR endocytosis. It is important to emphasize that for PIP3 accumulation it is necessary to turn off the main antagonist of PI3K – PTEN (phosphatase and tensin homolog deleted on chromosome 10). The reactive oxygen species (ROS) turn off PTEN what needed to realize the effect of insulin [5].

Conclusion: Incubation of slices in solution with the addition of insulin leads to impaired development and maintenance of long-term potentiation. The insulin effects did not with NMDA receptor and implemented in the presence of ROS.

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