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# AMPA receptors endocytosis pathways involve into complexity regulatory network of synaptic plasticity

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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 [1]. It mediated of intermolecular rearrangements and form the functional regulatory networks. In addition, the receptors of various hormones, in particular insulin, growth and neurotrophic factors, as well as the receptors of other mediator systems are present in the synaptic contact zone. However, the molecular mechanisms of links synaptic signalling pathways to the AMPARs endocytosis machinery remains elusive.
*Methods and Algorithms*: The interactome of hippocampal dendritic spines was reconstructed (technology GeneNet was used (РОСПАТЕНТ № 990006 от 15/02/1999)). Synaptic processes of the adult hippocampus have been reconstructed on the basis of GeneNet information (http://wwwmgs.bionet.nsc.ru/mgs/gnw/genenet/viewer) [2].
*Results*: The AMPAR is subject to functionally distinct constitutive and regulated clathrin-dependent endocytosis, contributing to various forms of synaptic plasticity. On induction of synaptic plasticity, internalized AMPA receptors undergo endosomal sorting and cycle through early endosomes and recycling endosomes back to the plasma membrane (model for long-term potentiation) or target for degradation to the lysosomes (model for long-term depression) [3]. The reception of the basic mediator signal – glutamat – is carried out by NMDAR macrocomplexes. NMDAR activation leads to clathrin-dependent endocytosis of postsynaptic AMPA receptors. 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). $Ca^{2+}$ influx through the NMDA receptor activates calcineurin and protein phosphatase 1 to dephosphorylate and activate phosphatidylinositol 4-phosphate 5-kinase (PIP5K), the major phosphatidylinositol 4,5-bisphosphate ($PI(4,5)P_2$)-producing enzyme in the brain [4]. PtdIns(4,5)P2 is a substrate for hydrolysis by phospholipase C (PLC). The products of the PLC catalyzation of PIP2 are inositol 1,4,5-trisphosphate (InsP3; IP3) and diacylglycerol (DAG), both of which function as second messengers. In this cascade, DAG remains on the cell membrane and activates the signal cascade by activating protein kinase C (PKC). GluR2-AMPAR, which provide the basic neurotransmission are move from the synaptic contacts zone after phosphorylation by PKC on S880 of GluR2 subunit cytoplasmic domain [5]. Metabotropic glutamate receptors I class, mGluR1 and mGluR5, involve in regulate of synaptic plasticity processes thru activate PLC [6].

PIP5K activation alternative pathway in the dendritic spine interactome during NMDAR-mediated synaptic plasticity was our reconstructed: ARF6 → PI(4)P5K alpha → PI(4,5)P2 (PIP2). PI(4)P5Kalpha is a downstream effector of ARF6 and when ARF6 is activated, it triggers recruitment of a diverse but interactive set of signaling molecules into sites of active cytoskeletal and membrane rearrangement, involved in on receptor-mediated endocytosis plasma, a membrane recycling pathway [7–9]. ARF6 activators, such as EFA6A, BRAG, are highly concentrated in the postsynaptic density fraction and formed a protein complex with NMDAR [10, 11]. BRAG2 regulates Arf6-dependent endocytosis of AMPARs through the direct interaction decrease in their synaptic expression in hippocampal neurons that kay during the hippocampal long-term depression [12]. 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 [13]. Insulin has also been shown to regulate the endocytosis of synaptic AMPA receptors [14]. Insulin effects mediated of PIP3 accumulation, that provides the prolonged of PKC activity and that contribute to 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 [15].

*Conclusion*: AMPAR endocytosis are key event during synaptic plasticity regulation. There are different and/or alternative pathways for triggering endocytosis of synaptic receptors, that is under the control of a complexity regulatory network in the dendritic spine interactome.

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