

Reconstruction of leptin and dopamin molecular counter-regulation in glutamatergic hippocampal synapses

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Motivation and Aim: Long-term potentiation increase density of AMPARs (The α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) at synaptic contact. In addition the receptors of various hormones, in particular leptin, growth and neurotrophic factors, as well as the receptors of other mediator systems, in particular, dopamine receptors, are present in the synaptic contacts zone. The hormone leptin crosses the blood brain barrier and regulates numerous neuronal functions, including hippocampal synaptic plasticity. The role of dopamine in the hippocampus remains poorly defined.

Results: The interactome of hippocampal dendritic spines was reconstructed (technology GeneNet was used (ROSPATENT No. 990006 from 15/02/1999)). After Long-term potentiation (LTP) a key event is the groundwork of second messenger's pools. $P4 \rightarrow PIP2$ (PtdIns(4,5)P₂) catalyzed Phosphoinositide 5-kinase (PI5K); $PIP2 \rightarrow PIP3$ (PtdIns(3,4,5)P₃) – Phosphoinositide 3-kinase (PI3K). PtdIns(4,5)P₂ is hydrolyzed at inositol 1,4,5-trisphosphate (InsP₃; IP₃) and diacylglycerol (DAG) by phospholipase C (PLC). DAG activates protein kinase C (PKC), that phosphorylates GluR2- and GluR1-AMPA. After that GluR2-AMPA move from and GluR1-AMPA incorporate at the synaptic contacts. Note GluR1-AMPA have to be phosphorylate of protein kinase A (PKA).

The activity of PKC is mediated by protein kinase PDK1 (3-phosphoinositide-dependent protein kinase 1) which binds to PtdIns(3,4,5)P₃. Thus, PIP₃ mediated a positive regulatory contour increasing the GluR1-AMPA synaptic density: $PIP2 \rightarrow PIP3 \rightarrow PDK1 \rightarrow PKC \rightarrow$ GluR1-AMPA incorporation. This counteracted by PTEN, which is observed when the basic synaptic activity takes place. After LTP induction leptin promotes the removal of PTEN and, thus, support the expression of GluR1-AMPA at the synapses. Dopamine trigger the cascade generation of cAMP that needed for activation of PKA. PKA phosphorylates of GluR1-AMPA too that critical for anchoring them on the plasma membrane of spines and for forming the pool of AMPA, which increases the density of synaptic AMPA after LTP induction.

Conclusion: A model in which the synaptic contact is represented not as a passive receiver of an input signal, but as a complexly organized multicomponent molecular system has been suggested. Leptin mediates the anchoring of AMPA at synapses. Dopamine is probably involved in the formation of a receptors pool that there may be rapid introduction to synapses after LTP induction.

Availability: <http://wwwmgs.bionet.nsc.ru/mgs/gnw/genenet/viewer/AMPA.html>

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