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Visualizing Memory Formation in the *Drosophila* Brain

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Long-term memory (LTM) formation requires time because information gradually accumulates across widely spaced learning episodes to a threshold that induces protein synthesis and synaptic changes. However, the neural mechanisms that determine this threshold remain obscure, particularly at the level of circuits. Here, we report that LTM formation from a one-time experience is prevented by induction of new proteins in a specific subset of neurons forming the mushroom body (MB), the learning and memory center in *Drosophila*. Blocking protein synthesis in early α/β MB neurons after a single training session induced LTM. Using a photoconvertible fluorescent protein KAEDE to report *de novo* protein synthesis, we have directly visualized learning-induced gene activation in a small subset of MB neurons, which increased the inhibitory constraints on the storage of LTM in the downstream circuits. We propose that learning induces sequential synthesis of new proteins at three distinct locations in the brain to inhibit, enhance, and consolidate LTM.

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Development of NR2A-subunit specific allosteric modulators

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Accumulating evidence suggests that depending on the subtypes and their subcellular localizations, NMDA receptors may exert differential functions on neuronal survival and death (Liu et al, Science 2004; Liu et al, J. Neurosci. 2007; Lai et al, Prog Neurobiol., 2014). Specifically, Synaptic NMDARs, which are predominantly NR2A-containing, promote neuronal survival through activation of neuronal cell survival signaling, whereas extrasynaptic NMDA receptors, which are preferentially NR2B-containing, are involved in mediating neuronal cell death, via activation of cell death signaling complexes. We therefore hypothesize that development of agents that can specifically potentiate NR2A containing receptors that either have no effect or even inhibit NR2B-containing NMDA receptors may represent novel neuroprotective therapeutics for reducing neuronal damages in neurodegenerative diseases such as HD.

The overall objective of this proposal is to identify novel, selective and potent modulators of the NR1/NR2A subtype of the NMDA receptor. We propose to achieve this by employing in silico modeling methods iteratively combined with in vitro experimental screening. We first, through a sequence alignment between NR2A and NR2B, identified potentially drug-able binding sites on NR2A subunit using various bioinformatics and in silico techniques. Druggability of these putative binding sequences were then evaluated on whether they can form a cavity suitable for a small molecule to bind and that the binding would ultimately cause conformational changes to induce an effect on glutamate or glycine binding to the receptor.

After the analysis, two binding sites were identified as being suitable to accommodate small molecules to bind. One binding site was located in the NR2A subunit, close to the glutamate binding site. This particular binding site was attractive because the binding pocket differed in volume quite extensively as compared with that in the NR2B. The second binding site is located in the interface between NR1 and the NR2A subunit. Interfaces are particularly important because there is a higher probability for them to induce conformational changes around the glycine co-agonist binding sites. Through computer-based chemical library screening and docking analysis, and following electrophysiological characterization of the chemicals with high docking scores in HEK cells overexpressing either NR1/NR2A or NR1/NR2B NMDA receptors, we have identified 2 types of chemical prototypes that can positive potentiate the NR1/NR2A subtype of the NMDA receptor. The first class of compounds are dual action drugs that can potentiate the function of NR1/NR2A subtype of the NMDA receptor and at the same time they can also inhibit that of NR1/NR2B subtype of the NMDA receptor. The second class of compounds can selectively potentiate the function of NR1/NR2A subtype, without affecting that of NR1/NR2B. Preliminary results further demonstrate that both classes of the chemicals significantly reduce NMDA-induced excitotoxic neuronal damages in cultured neurons.

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Biological Functions of Thrombomodulin

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Abstract

Thrombomodulin (TM) is a member of the group XIV family of C-type lectin-like domain containing glycoproteins. It was first identified as an endothelial trans-membrane glycoprotein which exhibits strong anticoagulant activity, since it can effectively promote protein C activation by thrombin. The activated protein C in complex with its specific receptor can catalyze the hydrolysis and degradation of coagulation factor Va and VIIIa to terminate blood coagulation cascade. In the subsequent reports TM protein expression was demonstrated in several different cell types including, keratinocytes, myeloid-derived monocytes and macrophages, and activated smooth muscle cells. Since some of these cell types do not have a direct contact with blood circulation, we proposed that TM might exhibit other novel important biological functions. Indeed, we and other labs demonstrated that TM is a multiple functional protein. We demonstrated that TM is participated in cell-cell adhesion and regulates epithelial-mesenchymal transition. The lectin-like domain of TM can regulate inflammatory response by binding to Le^y, lipopolysaccharide and high mobility group B1 protein. In the recent studies we demonstrated that TM expression is very important in the cell morphological change and differentiation of keratinocytes. We also demonstrated that TM is a novel receptor for plasminogen that can promote collective cell migration in endothelial cells and keratinocytes. Furthermore, the TM shedding in neo-epidermis is an essential factor contributing to wound healing process, indicating that TM protein can be applied to promote wound healing.