P1-g17 The effects of electrical stimulation of dorsal raphe nucleus on neuronal response properties of layer IV of barrel cortex following long-term sensory deprivation

Hamid Sheikhkanloui-Milan[1,2], Vahid Sheibani[1], Saeed Esmaeili-Mahani[3], Ali Shamsizadeh[4], Golamreza Sepehri[1], Mohammadreza Afarinesh[1]

[1] Kerman Neuroscience Research Center (KNRC), Kerman, Iran [2] Department of Physiology, School of Medicine, Ardebil University of Medical Sciences, Ardebil, Iran [3] Department of Biology, Faculty of Sciences, Shahid Bahonar University, Kerman, Iran [4] Department of Physiology, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran

Using single unit recording, the effect of electrical stimulation of dorsal raphe nucleus (DRN) on response properties of layer IV barrel cortex neurons following long-term sensory deprivation was evaluated. Sensory deprived (SD) and control (unplucked) groups were compared. In the SD group all but the D2 vibrissa were plucked on postnatal day one, and kept plucked for a period of 60 days. The spared D2 principal whisker (PW) and the deprived D1 adjacent whisker (AW) were deflected either singly or simultaneously, with neuronal responses being recorded from layer IV of the D2 barrel cortex. DRN was electrically stimulated at inter-stimulus intervals (ISIs) ranging from 0 to 800 ms before whiskers deflection. PW-evoked responses increased in the SD group with DRN electrical stimulation at ISIs 50 and 100 ms, whereas AW-evoked responses increased at ISI of 800 ms in both groups. Whisker plucking leads to increase in neuronal response of barrel cortex neurons to deflection of the PW and decreased responsiveness to deflection of the AW. DRN stimulation significantly reduced this difference in PW-evoked responses between groups. No response latency changes related to DRN stimulation were observed for PW or AW deflection in either group. Condition test (CT) ratio increased in SD rats, while DRN stimulation did not affect the CT ratio in both groups. The 5-HT2A receptor protein density did not change in barrel cortex of SD group compared to control. Data suggests that DRN electrical stimulation can modulate information processing in the sensory deprived barrel cortex.

doi:10.1016/j.neures.2010.07.1994

P1-n09 Protein-bound fragment based virtual screening (PFVS) approach to identify potential lead fragments as BACE1 inhibitors

Prabu Manoharan , Nanda Ghoshal

Structural Biology & Bioinformatics Division, Indian Institute of Chemical Biology, kolkata, India

BACE1 is an attractive and prominent target in Alzheimer's disease drug discovery efforts, because it catalyzes the rate limiting step of amyloid plaque formation one of the pathological hallmarks of Alzheimers disease. The traditional HTS approach which attempts to find potent small molecules against BACE1 results in lead candidates with high molecular weight and physical properties which contribute towards poor pharmacokinetic profile. Now it is apparent that targeting BACE1 poses great challenges for identifying small molecule that are both orally bioavailable and able to cross the blood–brain barrier. To meet this challenge of identifying optimal lead molecules, which will strike a balance between activity and oral bioavailability, blood–brain permeability, we report here a Computational Chemistry based Fragment Screening Approach (CC-FSA). This method combines the shape, electrostatic and pharmacophoric features of known fragment molecules, bound to protein conjugate crystal structure that aims to identify both chemically and energetically feasible small fragments that bind to BACE1 active site. To begin with, small molecular lead fragments bound to the BACE1 crystal structures deposited in PDB were used as seed-template to screen the drug like fragment databases, available with the OpenEye and MOE software. The obtained initial small molecular fragment hits were than rigidly docked into the BACE1 active site using Gold docking software in order to identify the interaction between the fragments and the active site. Once the crucial interaction between the fragments and binding site were identified, the hits were taken to the next step for filtering. The final prioritization of the top fragment hits were done by Poisson–Boltzman based free-energy calculation method available in the Syzbki program. The novel method employed in this study may serve as a starting point for the development of potential lead molecules for BACE1-directed Alzheimer's disease therapeutics.

doi:10.1016/j.neures.2010.07.1995

P1-n13 Amyloid precursor protein binding protein-1 modulates cell cycle progression of neural stem cells

Hee Jin Kim[1] , Yuyoung Joo[1], Bo-Hyun Hong[1], Sungji Ha[1], Jeong-A Kim[1], Keun-A Chang[1], Sun Woong[2], Sang Hyung Lee[3], Yoo-Hun Suh[1], Hye-Sun Kim[1]

[1] Dept. of Pharmacology, College of medicine, Seoul National University, Republic of Korea [2] Dept. of Anatomy, Korea University, School of Medicine, Seoul, Republic of Korea [3] Department of Neurosurgery, Seoul National University, College of Medicine, Seoul, Republic of Korea

Amyloid precursor protein binding protein-1 (APP-BP1) is one of proteins that bind to carboxyl terminus of the amyloid precursor protein (APP) and serves as the bipartite activation enzyme for the ubiquitin-like protein, NEDD8. The exogenous expression of APP-BP1 in neurons has been reported to cause DNA synthesis and consequent apoptosis via a signaling pathway that is dependent on APP-BP1 binding to APP. In addition, APP-BP1 is upregulated in the hippocampi of Alzheimers disease patients brains. In the present study, we explored the physiological role of APP-BP1 for cell cycle progression of fetal neural stem cells and found that cell cycle progression of the cells is arrested at the G1 phase by depletion of APP-BP1, which resulted in a marked decrease in the proliferation. Consistent with its critical function for cell cycle progression, the amount of APP-BP1 varies depending upon cell cycle phase, with culminating expression at S-phase. Furthermore, our FRET experiment revealed that phosphorylation of APP at threonine 668, known to occur during G2/M phase is required for the interaction between APP and APP-BP1. Collectively, these indicate that APP-BP1 plays an important role in cell cycle progression of fetal neural stem, likely through the interaction with APP which would be fostered by phosphorylation of threonine 668.

doi:10.1016/j.neures.2010.07.1996

P1-n15 Tyro 3 receptor reduce production of Aβ and prevent neuron damage in models of Alzheimer disease

Yan Zheng , Qi Wang, Xiao-min Wang

Department of Physiology, Capital Medical University, Beijing, China

Tyro 3 is a receptor tyrosine kinase and preferentially expressed in the central nervous system during neurogenesis and exhibits distinct expression patterns in adult brain, which are highly concentrated in the regions of neocortex and CA1, CA3 of hippocampus, and mainly associated with neurons. To date, there is no evident showing the function of Tyro 3 in neurodegenerative diseases. There has been found in our studies that Tyro 3 knockout mutants exhibited evident loss of neurons in cortex and hippocampus which are exactly the fields specifically expressing Tyro 3 in brain, and diminished hippocampal LTP as young adult and, when aged, they displayed move retardation and dementia. Moreover, we also found that Tyro 3 expression was regulated by NGF and associated to the differentiation of cholinergic neurons. In addition, Tyro 3 mediated the neurotrophic effects of its natural ligand on differentiating PC12 cells and primary hippocampal neurons. Firstly, to investigate the role of Tyro 3 receptor played in APP processing, which is the original source of Aβ, we established a cell line stably expressing humanized APP/PS1 mutants and then transfected the construct of Tyro 3 to the cell line. We found that overexpression of Tyro 3 reduced the production of Aβ and this effect was independent of its natural ligand, Gas6. Secondly, to study the role of Tyro 3 in the progression of neurodegeneration in AD, we cultured primary hippocampal neurons and induced the cells to degeneration and apoptosis by treatment of Aβ1–42 oligomer. Either Gas6 treatment or overexpression of Tyro 3 protected the primary neurons from the Aβ1–42 induced apoptosis. Finally, we bred APP/PS1 transgenic AD mice, APP/PS1; Tyro 3−/− mice. Some data suggested that the expression defect of Tyro 3 may be involved in the pathogenesis of AD.

doi:10.1016/j.neures.2010.07.1997

P1-s15 Superoxide flashes are modulated by ATP/ADP ratio and succinate

Wanrui Zhang

Institution of Molecular Medicine, Peking University, China

We have recently characterized a circularly permuted yellow fluorescent protein (cpYFP) as a specific superoxide indicator using an in vitro system, and discovered spontaneous transient bursts of superoxide generation (superoxide flash) within single mitochondria (Cell, 2008). To further emphasize the specificity of cpYFP as a probe for superoxide, two more in vivo experiments were conducted in adult rat cardiac myocytes expressing cpYFP