Neuropsin is associated with MAP2c dependent dendritic morphology in aging brain

Arpita Konar, Mahendra Kumar Thakur

Biochemistry and Molecular Biology Laboratory, Brain Research Centre, Department of Zoology, Banaras Hindu University, Varanasi 221 005, India

Correspondence: MK Thakur
E-mail: mkt_bhu@yahoo.com
Received: January 01, 2015
Published online: January 28, 2015

Brain aging associated impairment in synaptic plasticity and memory increases vulnerability for neurodegenerative pathologies. However, lacunae in understanding the molecular mechanisms underlying such impairment have hindered the development of recovery strategies. In this context, the emerging evidences for modifying the synaptic morphology by activity dependent plasticity proteases are noteworthy. Neuropsin (NP) is one such serine protease implicated in synaptic plasticity and memory acquisition, though it has never been explored in aging brain. Recently, we reported regional variation of NP expression in aging mouse brain. It was predominant in forebrain regions exhibiting age dependent decline in cerebral cortex, sharp increase in adult olfactory bulb and hippocampus and thereafter reduction in old age. The expression pattern of NP was strongly correlated with cleavage of its substrate, L1CAM and downstream dendritic marker MAP2c level in different brain regions during aging. In the present research highlight, we provide a brief overview of our laboratory findings related to brain aging with particular focus on NP expression and its implication in MAP2c dependent dendritic morphological changes. Such novel findings suggest NP as a potential therapeutic target for age associated decline in memory and related disorders.

Keywords: Brain Aging; Memory; Neuropsin; MAP2c; Dendritic morphology

To cite this article: Arpita Konar, et al. Neuropsin is associated with MAP2c dependent dendritic morphology in aging brain. Ther Targets Neurol Dis 2015; 2: e503. doi: 10.14800/ttnsd.503.

The aging brain entails a series of minor to extensive structural and functional changes leading to cognitive impairment and increase in the risk of neurodegenerative disorders, particularly Alzheimer’s disease (AD) [1]. Over the past years, our laboratory focus has been to investigate the AD candidate genes in the course of normal brain aging process. The expression of amyloid precursor protein (APP) mRNA responsible for accumulation of amyloid beta peptide in AD brain showed significant increase in the cerebral cortex of old mice [2]. Presenilin (PS) genes, responsible for early onset AD, showed downregulation of PS1 but upregulation of PS2 expression in old mouse cerebral cortex [3]. Apolipoprotein E (apoE) gene coding for lipid transport protein and considered as a risk factor for sporadic and familial AD showed higher expression in young as compared to adult and then remained unaltered in old mouse cerebral cortex [4]. Some of these alterations were regulated by sex steroids, estrogen and androgen. The level of steroid receptors, coregulators as well as ligand declined during aging leading to altered downstream signaling cascade and gene expression [5].

As enormous evidences have accumulated from human and animal models revealing that brain aging alterations are attributed to neuronal morphology and synaptic connectivity [6], we were interested to explore the genes influencing these processes. Moreover, these changes occur in a region specific manner with forebrain areas of frontal cortex and
hippocampus being primarily affected than others. Little is known at molecular level to account for such selective regional vulnerability [7, 8]. There are few studies highlighting the involvement of neuronal activity induced secretion of certain proteases in the synaptic cleft and cleaving the extracellular matrix molecules leading to regulation of neuronal morphology and synaptic connectivity [9, 10]. However, these proteases have gained limited attention in the process of brain aging.

Neuropsin (NP), also known as KLK8, is one such serine protease of the kallikrein (KLK) family that was originally identified from mouse hippocampus [11]. Its expression was predominant in neurons of hippocampal CA1-CA3 sub regions, amygdala and moderate in prefrontal cortex [12, 13]. NP gets induced by neural activity and cleaves few cell adhesion molecules in the synaptic cleft. Among them, cleavage of L1CAM, an immunoglobulin superfamily neural cell adhesion molecule, is implicated in dynamic rearrangement of the morphology and plasticity of schaffer collateral synapses [14]. L1CAM also influences growth of dendrites of hippocampal neurons by inducing the expression of microtubule associated protein (MAP) 2c [15]. In animal experiments, NP gene deficiency causes severe impairments in LTP and spatial memory [16, 17].

These compelling evidences intrigued us to explore NP and its effectors L1CAM and MAP2c in different regions of aging mouse brain. We showed that NP is expressed primarily in forebrain regions of olfactory bulb, cerebral cortex and hippocampus throughout the life span except in medulla oblongata where prominent expression was found only at young age. This observation was not consistent with earlier report which considered NP as a limbic region specific protease [11]. Besides regional differences, NP expression significantly varied in different age groups. NP mRNA and protein expression was markedly reduced in the forebrain regions of olfactory bulb, cerebral cortex and hippocampus of old mice as compared to young. In cerebral cortex, NP showed gradual decline with age whereas in olfactory bulb and hippocampus there was a drastic increase in adult and thereafter reduction in old. As these brain regions are pivotal for memory and cognition, even subtle alterations in neuronal population might lead to cognitive impairment [6, 18, 19]. Therefore, NP might be a molecular determinant of region specific neuronal vulnerability and consequent decline in memory during aging.

Another striking observation of our study was remarkable increase of NP expression in adult olfactory bulb and hippocampus, which are considered potent regions for adult neurogenesis [20, 21]. The incorporation of new functional neurons into existing neural networks provides a higher capacity for synaptic plasticity, which may favor the encoding and storage of certain types of memories [22, 23]. Therefore, it is likely that NP might be directly involved in neurogenesis or subsequent processes of neuronal differentiation and neurite growth. Further, we analyzed L1CAM cleavage and downstream MAP2c protein level in NP expressing brain regions of aging mice. Interestingly, we observed a regional as well as age dependent strong positive correlation of L1CAM cleavage and downstream MAP2c level with NP expression pattern [24]. These findings implicated that NP secretion into the synaptic cleft cleaves L1CAM that either gets translocated to nucleus or activates intracellular signaling cascades which in turn increases MAP2c expression and dependent dendritic growth. In order to confirm this speculation, we performed siRNA mediated NP gene silencing and analyzed MAP2c stained primary hippocampal neurons. NP silencing markedly reduced length and branching of MAP2c positive dendrites (unpublished). Overall, our findings suggest that age dependent regional variation in NP expression and its correlation with dendritic marker MAP2c might account for alterations in dendritic morphology with associated synaptic plasticity and memory during aging.

Acknowledgement

The work cited from author’s laboratory was supported by grants from the Department of Science and Technology, Indian Council of Medical Research and Department of Biotechnology, Government of India to MKT.

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