Phosphatidylethanolamine-Binding Protein 1 (PEBP1) as a Potential Target for the Treatment for Depression

Yang Sun, Zhu-Min Luo, Min-Jun Zheng & Xia Liu

Department of Pharmacology, School of Pharmacy, Second Military Medical University, Shanghai, China

Correspondence

Xia Liu, Department of Pharmacology, School of Pharmacy, Second Military Medical University, 325 Guo-He Road, Shanghai 200433, China.

Tel.: +86-21-81871280;

Fax: +86-21-65493951;

E-mail: lxfling@aliyun.com

Received 25 August 2013; revision 15

September 2013; accepted 17 September 2013

doi: 10.1111/cns.12185

The first two authors contributed equally to this work.

Depression is a severe neuropsychiatric disorder, which can have a negative effect on people's thoughts, behavior, world view, and both mental and physical well being. It not only harms the health of the patients, but also puts their families and the whole society in danger [1]. Hippocampal dysfunction is widely reported to be associated with the occurrence of depression [2]. However, the underlying molecular mechanism remains largely unknown.

In the current study, we compared protein expression profile of the hippocampus between normal and spontaneously depressed cynomolgus monkeys (National Nonhuman Primates Animal Center, Suzhou, China), which have more behavioral and physiological characteristics in common with human. All animals were used in accordance with the guidelines of Second Military Medical University for Animal Care. The animals were anesthetized before sacrificed.

As shown in Figure 1A, the 2-D DIGE comparison of hippocampus proteins showed some proteins up-regulated (spots labeled

red) and some proteins down-regulated (spots labeled green) in depressed monkeys as compared to the normal control. Eight different expressed protein spots were identified by mass spectrometry. Interestingly, both spot 1 (down-regulated in depressed monkey) and spot 2 (up-regulated in depressed monkey) were identified as phosphatidylethanolamine-binding protein 1 (PEBP1) (2-D gel electrophoresis, Figure 1B). PEBP1, also known as precursor protein of hippocampal cholinergic neurostimulating peptide (HCNP-pp) or Raf kinase inhibitor protein (RKIP), is principally localized in hippocampus. Previous proteomic analysis of rat hippocampus after chronic treatment with antidepressants revealed up-regulation of total PEBP1 protein [3]. Kim et al. [4] also reported that total PEBP1 mRNA and protein expression are decreased in rat hippocampus after stress exposure. However, Matsukawa et al. found that PEBP1 transgenic mice showed a depressive-like phenotype at 30 weeks of age [5]. The relationship between PEBP1 and depression remains controversial.

Figure 1 The different expression of PEBP1 between the control and depressed monkeys. (A) Left shows the 2-D DIGE comparison of hippocampus proteins derived from control (Cy3, green) or depressed (Cy5, red) monkeys. Right shows the indicated spots at higher magnification. (B) The 2-D gel electrophoresis of hippocampus proteins derived from control (left) or depressed (right) monkeys. Arrows indicate spots identified as PEBP1.

Figure 2 PEBP1 expresses in different forms between the control and depressed monkeys. Western blotting of PEBP1 (A) and p-PEBP1 (Ser-153) (B) in the cerebral cortex and hippocampus proteins obtained from control or depressed monkeys.

We further verified the different expression level of PEBP1 between the normal control and the depressed monkey by Western blotting (Figure 2). Total PEBP1 increased (Figure 2A), while phosphorylated PEBP1 (Ser-153) decreased (Figure 2B) in the depressed monkey compared with the normal control. As previously reported, PEBP1 phosphorylation at Ser-153 by PKC causes release of PEBP1 from Raf-1, then activates ERK cascade [6]. ERK is an important molecule involved in depression. Reduced activation and expression of ERK were detected in the postmortem brains of depressed suicide subjects [7]. And ERK phosphorylation has also been hypothesized as an intracellular signaling mechanism mediating antidepressant efficacy [8]. In our results, decreased level of PEBP1 phosphorylation at Ser-153 in depressed monkeys indicates the reduced activation of ERK, which may promotes the occurrence of depression.

As precursor protein of HCNP, the increased total PEBP1 level may result in the increased level of HCNP, which is an 11 amino-acid peptide and can induce the synthesis of acetylcholine by increasing the amount of choline acetyltransferase (ChAT) in the medial septal nucleus [9]. Previous studies have reported cholinergic hypersensitivity in depression and neuronal nicotinic acetylcholine receptor antagonists are associated with antidepressant effects [10]. The increased PEBP1 or HCNP may evoke depressive-

like phenotype by over-exposure of the central nervous system to acetylcholine. In this assumption, the Spot 2 (Figure. 1) may be the cleaved PEBP1. Besides the cleaving and the phosphorylation form of PEBP1, there may be other post-transcriptional modification of PEBP1 related to depression, which needs further investigation.

In summary, we found a protein named PEBP1, which expresses differently in the depressed monkey compared with the normal control. And further elucidation of the mechanisms behind PEBP1 post-transcriptional modification may tie the controversy about PEBP1 and depression and will also provide a new insight into the field of exploring new antidepressant drugs.

Acknowledgments

This work was supported by Grants from the 973 National Key Basic Research Program of China (2009CB521901, to Ding-Feng Su) and National Natural Science Foundation of China (No. 30973525, No. 81273606 to Xia Liu).

Conflict of Interest

The authors declare no conflict of interest.

Reference

- Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004;116:281–297.
- Lee Y, Ahn C, Han J, et al. The nuclear RNase III Drosha initiates microRNA processing. *Nature* 2003;425:415–419.
- Khawaja X, Xu J, Liang JJ, Barrett JE. Proteomic analysis of protein changes developing in rat hippocampus after chronic antidepressant treatment: Implications for depressive disorders and future therapies. *J Neurosci Res* 2004;75:451–460.
- Kim HG, Kim KL. Decreased hippocampal cholinergic neurostimulating peptide precursor protein associated with stress exposure in rat brain by proteomic analysis. *J Neurosci Res* 2007;85:2898–2908.
- Matsukawa N, Furuya Y, Ogura H, Ojika K. HCNP precursor protein transgenic mice display a depressive-like phenotype in old age. *Brain Res* 2010;1349:153–161.
- Corbit KC, Trakul N, Eves EM, Diaz B, Marshall M, Rosner MR. Activation of Raf-1 signaling by protein kinase C through a mechanism involving Raf kinase inhibitory protein. *J Biol Chem* 2003;278:13061–13068.
- Dwivedi Y, Rizavi HS, Roberts RC, Conley RC, Tamminga CA, Pandey GN. Reduced activation and expression of ERK1/2 MAP kinase in the post-mortem brain of depressed suicide subjects. *J Neurochem* 2001;77:916–928.
- Gourley SL, Wu FJ, Kiraly DD, et al. Regionally specific regulation of ERK MAP kinase in a model of antidepressant-sensitive chronic depression. *Biol Psychiatry* 2008;63:353–359.
- Uematsu N, Matsukawa N, Kanamori T, et al. Overexpression of hippocampal cholinergic neurostimulating peptide in heterozygous transgenic mice increases the amount of ChAT in the medial septal nucleus. *Brain Res* 2009;1305:150–157.
- Andreasen JT, Olsen GM, Wiborg O, Redrobe JP. Antidepressant-like effects of nicotinic acetylcholine receptor antagonists, but not agonists, in the mouse forced swim and mouse tail suspension tests. *J Psychopharmacol* 2009;23:797–804.