Concerning HB-EGF Brain Levels in Schizophrenia: Cellular Distribution of Putative Sheddases May Matter

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We read the recent article of Hoyagi and Hara [1] in the reviews section with great interest and would like to comment for a particular aspect of their interesting overview on the multiple roles played by heparin-binding EGF-like growth factor (HB-EGF) in the developing and adult CNS, namely the potential implication of HB-EGF for the pathophysiology of schizophrenia. Referring to our article on ADAM12 and schizophrenia [2] Oyagi and Hara correctly state that “ectodomain shedding of HB-EGF, regulated by ADAM, is critical for its functioning. According to the recent report, the density of ADAM12 immunoreactive oligodendrocytes was decreased in the white matter of the anterior cingulate cortex of schizophrenia patients. The ADAM12 gene is located on human chromosome 10q26.3, which has been linked to schizophrenia. These decreased expressions of ADAM family proteases might affect the activity of HB-EGF in the brain of schizophrenia patients, and the alterations affecting HB-EGF signaling could compromise a contributing factor to psychiatric disorders”. Indeed, the assumption of reduced levels of HB-EGF in brains of schizophrenics would help to explain certain disease-related abnormalities in EGF- and neuregulin-ErbB1, ErbB4 signaling as well as impaired neurogenesis [1]. Moreover, ventral forebrain-specific HB-EGF conditional knock-out mice show a schizophrenia-like behavior with increased locomotor activity, decreased social interaction activity, impairment of prepulse inhibition, and deficits in object recognition and memory [3]. Unfortunately, however, HB-EGF brain levels have been reported to be normal and not decreased in schizophrenia [4]. How to resolve this contradiction? First of all, it should be mentioned that besides ADAM12 there are other established or proposed HB-EGF sheddases that belong to the ADAM family, including ADAM17, ADAM9, and, possibly, ADAM10 [5,6]. Importantly, unlike ADAM12, the other putative HB-EGF sheddases are predomi-

nantly expressed in neurons. As HB-EGF is highly expressed both in neurons and parafascicular oligodendrocytes [7], a certain “division of business” may take place: ADAM9, 10 and 17 probably shed neuronal HB-EGF, while ADAM12 does the same with HB-EGF generated by oligodendrocytes. Interestingly, “neuronal” HB-EGF sheddases are upregulated in schizophrenia [8,9] and only the oligodendroglia-located sheddase ADAM12 is downregulated [2]. Consequently, there should be enough sheddase capacity in brain gray matter in patients with schizophrenia to guarantee normal HB-EGF levels in these areas. And this is exactly what was measured by Futamura et al. [4], when they studied different gray matter regions dissected from schizophrenia brains. Unfortunately, there is yet no information about HB-EGF concentrations in white matter areas of schizophrenics, but given a white matter sheddase deficit in schizophrenia (due to reduced ADAM12 expression), HB-EGF levels might indeed be lower in this brain compartment—with fatal consequences for the development/maturation of oligodendrocytes and myelin composition as shown to be typical for schizophrenia (reviewed in [10]). Moreover, due to the known autocrine, juxtacrine and paracrine mode of action of HB-EGF, it is well conceivable that HB-EGF mainly operates in circumscribed spatial domains rather than traveling long distances, thus possibly precluding an equalisation of concentrations between gray and white matter. This scenario, however, remains speculative, until white matter HB-EGF concentrations have been measured in postmortem brains of subjects with schizophrenia.

Conflict of Interest

The authors declare no conflict of interest.

References

- Oyagi A, Hara H. Essential roles of heparin-binding epidermal growth factor-like growth factor in the brain. *CNS Neurosci Ther* 2012;**18**:803–810.
- Farkas N, Lendeckel U, Dobrowolny H, et al. Reduced density of ADAM 12-immunoreactive oligodendrocytes in the anterior cingulate white matter of patients with schizophrenia. *World J Biol Psychiatry* 2010;**11**:556–566.
- Oyagi A, Oida Y, Kakefuda K, et al. Generation and characterization of conditional heparin-binding EGF-like growth factor knockout mice. *PLoS ONE* 2009;**4**:e7461.
- Futamura T, Toyooka K, Iritani S, et al. Abnormal expression of epidermal growth factor and its receptor in the forebrain and serum of schizophrenic patients. *Mol Psychiatry* 2002;**7**:673–682.
- Sahin U, Weskamp G, Kelly K, et al. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. *J Cell Biol* 2004;**164**:769–779.
- Hinkle CL, Sunnarborg SW, Loisel D, et al. Selective roles for tumor necrosis factor alpha-converting enzyme/ADAM17 in the shedding of the epidermal growth factor receptor ligand family: the juxtamembrane stalk determines cleavage efficiency. *J Biol Chem* 2004;**279**:24179–24188.
- Nakagawa T, Sasahara M, Hayase Y, et al. Neuronal and glial expression of heparin EGF-like growth factor in central nervous system of prenatal and early-postnatal rat. *Brain Res Dev Brain Res* 1998;**108**:263–272.
- Marballi K, Cruz D, Thompson P, Walss-Bass C. Differential neuregulin 1 cleavage in the prefrontal cortex and hippocampus in schizophrenia and bipolar disorder. *PLoS ONE* 2012;**7**:e36431.
- Vawter MP, Atz ME, Rollins BL, Cooper-Casey KM, Shao L, Byerley WF. Genome scans and gene expression microarrays converge to identify gene regulatory loci relevant in schizophrenia. *Hum Genet* 2006;**119**:558–570.
- Bernstein HG, Steiner J, Bogerts B. Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy. *Expert Rev Neurother* 2009;**9**:1059–1071.