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REVIEW

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Essential Roles of Heparin-Binding Epidermal Growth Factor-Like Growth Factor in the Brain

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SUMMARY

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a member of the EGF family of growth factors, which interacts with the EGF receptor to exert mitogenic activity for various types of cells. Through its interactions with various molecules, it is involved in diverse biological processes, including wound healing, blast implantation, and tumor formation. At the same time, HB-EGF is widely expressed in the central nervous system, including the hippocampus and cerebral cortex, and is considered to play pivotal roles in the developing and adult nervous system. Because HB-EGF protein levels in the brain are much higher than those of TGF-α and EGF, it is possible that HB-EGF serves as a major physiologic ligand for the EGF receptor (ErbB1) within the central nervous system. Recent studies indicate that HB-EGF contributes to the neuronal survival and proliferation of glial/stem cells. HB-EGF also promotes the survival of dopaminergic neurons, an action mediated by mitogen-activated protein kinase (MAPK) as well as by the Akt signaling pathway. In this review, we discuss recent findings on the implications of HB-EGF in higher brain functions of the central nervous system.

Introduction

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) is a member of the EGF family of growth factors, which includes EGF, transforming growth factor (TGF)-α, amphiregulin, betacelulin, and neuregulin [1–3]. HB-EGF is a 22-kDa, O-glycosylated protein, which was isolated from the conditioned medium of a human macrophage-like cell line in 1991 [2]. HB-EGF and amphiregulin can be distinguished from other members of the EGF family by the presence of a heparin-binding domain, which interacts with membrane-bound heparin sulfate proteoglycans and may thereby regulate EGF receptor activation. HB-EGF binds to and activates the EGF receptor (EGF receptor/ErbB1) [2] and ErbB4 [4] to exert mitogenic, chemoattractant, and cell survival activities. Among the members of the EGF family, HB-EGF knockout (KO) mice die shortly after birth [5,6], whereas KO mice for the other EGF family growth factors, such as EGF, TGF-α, amphiregulin, and epiregulin, do not die in that manner and have different phenotypes [7–9]. These results suggest that of all the members of the EGF family, HB-EGF plays the most roles in growth and development.

Heparin-binding epidermal growth factor is initially synthesized as a membrane-anchored precursor protein (proHB-EGF), similar to other EGFR ligands [2]. HB-EGF and amphiregulin could be distinguished from other members of the EGF family by the presence of a heparin-binding domain, which interacts with membrane-bound heparin sulfate proteoglycans and may thereby regulate EGF receptor activation. ProHB-EGF is cleaved by metalloproteases, known as a disintegrin and metalloproteases (ADAMs), to yield the soluble form of HB-EGF (sHB-EGF), through a process known as ectodomain shedding [2,10]. sHB-EGF binds to and activates the EGF receptor (ErbB1) [2] and ErbB4 [4] to exert a potent mitogen and chemoattractant for a number of different cell types [3]. On the other hand, the carboxyl terminal fragment of HB-EGF (HB-EGF-CTF) generated by ectodomain shedding translocates to the nucleus by endocytosis. Subsequently, HB-EGF-CTF exerts effects on the regulation of cell proliferation by binding the nuclear promyelocytic leukemia zinc finger (PLZF) protein, a transcriptional repressor, causing its nuclear export [11]. PLZF exerts transcriptional repression through decreased expression of cyclin A. Through these two different pathways, HB-EGF exerts its physiological functions. Furthermore, forms of proHB-EGF associate with several molecules, such as CD9 integrin α3β1 and heparan-sulfate proteoglycan to modulate their biological activity [12]. In addition, proHB-EGF functions as the sole receptor for the diphtheria toxin in humans, mediating the entry of the diphtheria toxin into the cytoplasm [13,14]. The diphtheria toxin binds to human HB-EGF, but not to mouse HB-EGF, because of the difference of amino acid sequence between human and mouse in the EGF-like domain, which is responsible for the binding of diphtheria toxin with HB-EGF [15].

Many studies have demonstrated the importance of HB-EGF in diverse biological processes, including wound healing [16–18], blast implantation [19], atherosclerosis [20], heart development [5,6,21], and tumor formation [22], through the activation of the signaling molecules downstream of ErbB receptors and interactions with molecules associated with HB-EGF. In particular, HB-EGF has been implicated in tumor progression because of its altered expression in many tumors, including hepatocarcinoma [23], colon [24], breast [25,26], prostate [27], and bladder tumors [28,29]. Cross-reacting material 197 (CRM197), a specific inhibitor of HB-EGF, showed a remarkable suppression of tumor growth [30], and a clinical trial of CRM197 in patients with advanced cancer also showed a promising antitumor effect [31,32]. These results suggest that HB-EGF would be a likely target for cancer therapy.

Meanwhile, HB-EGF is widely expressed in the central nervous system, including the hippocampus and cerebral cortex, and is considered to play pivotal roles in the developing and adult nervous system [33–35]. Previous studies indicate that HB-EGF contributes to the neuronal survival and glial/stem cells proliferation [34,36,37]. HB-EGF also promotes the survival of dopaminergic neurons, an action mediated by MAPK as well as by the Akt signaling pathway [37]. In this review, we discuss recent findings on the implication of HB-EGF in higher brain functions in the central nervous system. In particular, we focused on the biological functions of HB-EGF on psychomotor behavior, cerebral ischemia, nigrostriatal dopaminergic neuron, memory, and synaptic plasticity (Figure 1 and Table 1).

Expression of HB-EGF in the Central Nervous System

In the central nervous system, HB-EGF is highly expressed in neurons, as well as astrocytes and oligodendrocytes [34]. *In situ* hybridization and immunohistochemical analysis reveals that HB-EGF mRNA and proteins are distributed throughout the brain, in sites such as the cerebral cortex, hippocampus, thalamus, hypothalamus, basal ganglia, midbrain, olfactory bulb, and so on [34]. The level of HB-EGF expression is much higher in brains of young animals than in adult brains, which implies its marked function during early developmental stages [38]. On the other hand, the expression of EGF receptors (ErbB1, ErbB2, ErbB3, and ErbB4) varies among different types of neurons, widely distributed in the brain, and play a major role under both physiological and pathological conditions [39]. ErbB1 is enriched in the neocortex, striatum, and hippocampus and has been proposed to contribute to the development of the central nervous system [40]. ErbB4 receptor mRNA also includes the cortex, amygdala, hippocampus, medial habenula, reticular thalamic nucleus, several hypothalamic nuclei, subthalamic nucleus, substantia nigra pars compacta, and the ventral tegmental area (VTA) [41]. Also, astrocytes express HER1/ErbB1 and maybe small amounts of HER4/ErbB4 [36,42]. HER4/ErbB4 has been detected at high levels in the postsynaptic density, indicating the possibility of its involvement in synaptic plasticity [43].

Among ErbB1 ligands, HB-EGF protein levels were much higher in several brain regions, such as the cerebral cortex, striatum, thalamus, and so on than those of the TGF-α and those of EGF were the lowest [44]. It is possible that HB-EGF serves as a major physiologic ligand for the EGF receptor within the central nervous system. These localizations of the HB-EGF and EGF receptors indicate that the HB-EGF signal may be an important trophic factor in the developing central nervous system and a contributor to higher brain functions.

Activity-dependent shedding of HB-EGF was also observed in neuronal cells, as in other types of cells [45]. Several neurotransmitters, such as glutamate, kainate, and *N*-methyl-D-aspartate (NMDA), trigger the ectodomain shedding of proHB-EGF in neuron-enriched cortical and hippocampal cultures [45]. Metalloproteinases in the ADAM family play prominent roles in the shedding of proHB-EGF induced by these neurotransmitters in neurons and glia [45]. Individual ADAM isoforms showed strikingly different expression in the central nervous system [45,46]. For instance, ADAM10 and ADAM 17 (TACE) were expressed in the hippocampus, neocortex, and cerebellum [46], while ADAM11 mRNA was present throughout the forebrain [47]. Accordingly, the region-specific expression pattern of ADAM isoforms might precisely regulate the action of HB-EGF and other EGF families.

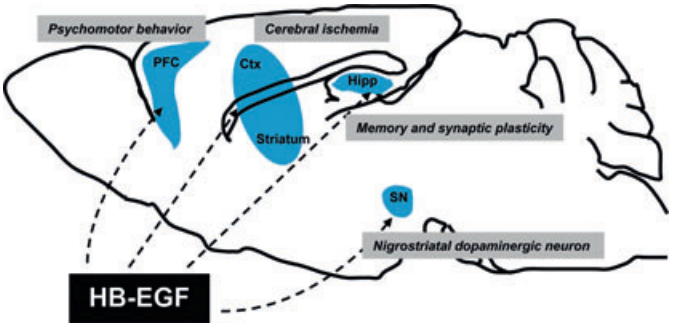

Figure 1 Roles of heparin-binding epidermal growth factor (HB-EGF) in the central nervous system and higher brain function. HB-EGF is widely expressed throughout the brain, in areas such as the cerebral cortex, hippocampus, thalamus, hypothalamus, basal ganglia, midbrain, olfactory bulb, and so on. In this review, we discuss recent findings on the implications of HB-EGF on psychomotor behavior, cerebral ischemia, nigrostriatal dopaminergic neuron, memory, and synaptic plasticity. PFC, prefrontal cortex; Hipp, hippocampus; SN, substantia nigra; Ctx, cortex.

Table 1 Biological function of heparin-binding epidermal growth factor (HB-EGF) in several pathological conditions

Condition	Species	Experimental findings	References
Psychiatric disorder	Mice	Forebrain specific HB-EGF knockout (KO) mice exhibited several behavioral abnormalities	[51]
Memory	Mice	Forebrain specific HB-EGF KO mice impaired memory formation and hippocampal long-term potentiation	[66]
Cerebral ischemia	Rat/Mice	HB-EGF expression was increased after focal cerebral ischemia	[81,84]
	Rat	Intraventricular administration of HB-EGF reduced infarct size after focal cerebral ischemia	[80]
	Rat	Gene transfer of HB-EGF enhanced neurogenesis and angiogenesis after focal cerebral ischemia	[93]
	Mice	Forebrain specific HB-EGF KO mice show exacerbated ischemia and reperfusion injury	[81]
Parkinson's disease	Rat	Intracerebral injection of HB-EGF protected the nigrostriatal dopaminergic system in an *in vivo* adult rat model of Parkinson's disease	[109]
	Human	HB-EGF level was not significantly altered in the patients of Parkinson's disease	[108]

Roles of HB-EGF in Psychomotor Behavior and Neuronal Transmission

Recently, neurotrophic and growth factor have been shown to be associated in psychiatric disorders, such as schizophrenia, bipolar disorder, and depression [48,49]. Abnormal development of the brain is implicated in the etiology and/or pathology of various psychiatric diseases. Similarly, psychiatric patients can display abnormalities in the expression of cytokines and neurotrophic factors. EGF protein levels have been found to be lower in the prefrontal cortex and striatum of schizophrenic patients [50]. Serum EGF levels were also lower in these patients, whereas EGF receptor expression in the prefrontal cortex was elevated [50]. These reports suggest that EGF signals may be associated with the pathogenesis of psychiatric disorders.

Ventral forebrain-specific HB-EGF conditional KO mice exhibited some behavioral abnormalities, such as increased locomotor activity, decreased social interaction behavior, impairment of prepulse inhibition (PPI), and deficit of object recognition and short-term memory [51]. Additionally, treatments with either a typical or an atypical antipsychotic drug ameliorated these behavioral impairments in HB-EGF KO mice. A typical antipsychotic (haloperidol) reduced the locomotor activity of HB-EGF KO mice, but not the social withdrawal or the deficit of PPI [51]. In contrast, atypical antipsychotics (clozapine and/or risperidone) ameliorated the impairments of social interaction and PPI. Generally, in animal models of psychiatric disorders, abnormal behaviors are accompanied by altered monoamine levels. In the prefrontal cortex, dopamine, 5-HT, and its metabolite 5-hydroxyindole acetic acid (5-HIAA) levels were decreased in HB-EGF KO mice. Similarly, various monoamine contents were also changed in other brain regions of HB-EGF KO mice, such as the striatum, cerebellum, and thalamus [51]. The dopamine hypothesis of schizophrenia has proposed that hyperactivity of dopamine transmission in the striatal dopamine system is responsible for the positive symptoms [52], while a deficit in dopamine transmission in the prefrontal cortex might be implicated in the cognitive impairments and negative symptoms of schizophrenia [53,54]. Abnormal development of the brain is implicated in the etiology and/or pathology of various psychiatric disorders. In schizophrenic patients, spine density in deep layer 3 prefrontal cortical pyramidal neurons is decreased compared with normal controls [55]. Behavioral deficits of HB-EGF KO mice are also accompanied with decreased spine density on the apical dendrites of the layer III pyramidal neurons (Figure 2) and NR1 protein of the NMDA receptor in the prefrontal cortex [51]. On the other hand, activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and p21-activated kinase (PAK) was markedly reduced in the prefrontal cortex of HB-EGF KO mice [51]. Overall, HB-EGF KO mice exhibited the behavioral abnormalities reflected in a comprehensive spectrum of psychomotor and cognitive dysfunctions, similar to many psychiatric disorders. HB-EGF KO mice also showed some neurological and neurochemical changes, which were relevant to the pathogenesis of schizophrenia. Meanwhile, genetically modified mouse for other EGF receptor ligands, such as EGF and TGF-α, have not been reported to show phenotypes of psychiatric disorders.

Contrary to the change of EGF expression in schizophrenia patients, there have been no reports about the relationship of psychiatric disease and the *Hb-egf* gene. Typically, HB-EGF is processed from its precursor protein, pro-HB-EGF, which is susceptible to proteolytic cleavage, namely ectodomain shedding, and is converted to the mature secreted factor [56]. Ectodomain shedding of HB-EGF, regulated by ADAM, is critical for its function. According to the recent report, the density of ADAM12 immunoreactive oligodendrocytes were decreased in the white matter of the anterior cingulate cortex of schizophrenic patients [18]. The ADAM12 gene is located on human chromosome 10q26.3, which has been linked to schizophrenia. These decreased expressions of ADAM family kinase might affect the activity of HB-EGF in the brains of schizophrenia patients and the alterations affecting HB-EGF signaling could comprise a contributing factor to psychiatric disorders. Meanwhile, EGF administration to neonatal rat induced some behavioral abnormalities in PPI, latent inhibition of learning, social interaction, and methamphetamine sensitivity [57]. All of these findings indicate that an abnormal EGF receptor signal on the neonatal stage may contribute to the

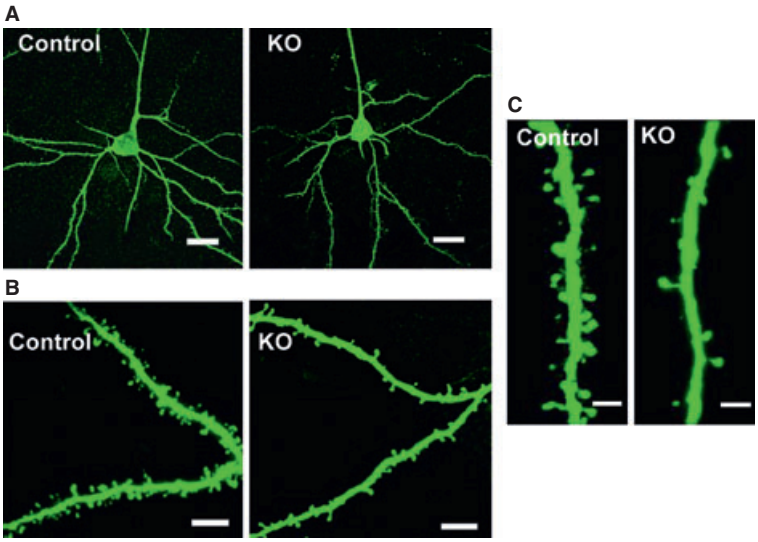

Figure 2 Morphological changes in the prefrontal cortex of ventral forebrain-specific heparin-binding epidermal growth factor (HB-EGF) knockout (KO) mice. (**A**) Representative photomicrographs showing morphology of pyramidal neurons in cortical layer III of the prefrontal cortex from wild-type control (left) and KO (right) mice. Scale bar = 20 μm. (**B**) Representative photomicrographs of apical dendritic segments from wild-type control (left) and KO (right) mice. Scale bar = 8 μm. (**C**) High-magnification images of apical dendritic segments from wild-type control (left) and KO (right) mice. Scale bar = 2 μm. These figures were reproduced from Oyagi et al. [51].

pathology of a number of psychiatric diseases, partly through perturbing normal brain development.

On the other hand, neuregulin-1 (NRG-1), another member of the EGF family, has been shown to be associated with schizophrenia in several different populations [58,59]. NRG-1 binds to the ErbB family of tyrosine kinase transmembrane receptors (ErbB4). Dysfunction of NRG-1 and ErbB4 signaling has been shown to participate in the pathophysiology of schizophrenia, partly through the NMDA receptor hypofunction [60,61]. HB-EGF also binds to the ErbB4 type of EGF receptor, but little is known about the function of HB-EGF and ErbB4 signaling in the central nervous system. Further studies, focused on the role of HB-EGF in the ErbB4 receptor in the central nervous system, could provide the proof for a causal link between HB-EGF and schizophrenia.

Roles of HB-EGF in Neuronal Growth and Synaptic Plasticity in the Hippocampus

In the brain, EGF family members act as neurotrophic molecules, serving to enhance stem cell proliferation and neural differentiation, and they also influence synaptic plasticity [62,63]. HB-EGF has been implicated in neuronal survival, glial/stem cell proliferation, and differentiation. HB-EGF also enhances the neurite outgrowth and neuroprotection against ischemic injury in PC12 cells by activation of the MAPK signal pathway [64]. In the hippocampus of the postnatal early stage (from P0 to P7), HB-EGF mRNA is distributed within all principle cell layers of the hippocampus, including stratum pyramidal fields CA1–CA3 and the stratum granulosum of the dentate gyrus, whereas by P14 and through adulthood, the expression in the pyramidal cell layer (CA1–3) was decreased substantially, but in the dentate gyrus, the layer remained higher [38]. Another report also suggests that HB-EGF contributes to adult neurogenesis in the dentate gyrus of the hippocampus [65]. These reports suggest that HB-EGF may be one of the important contributors to neuronal development and synaptic plasticity in the hippocampus.

The HB-EGF mRNA level was elevated in the hippocampus after kainate-induced excitotoxic seizures. In these conditions, HB-EGF protects the neurons against kainate toxicity in hippocampal cell cultures without affecting intracellular Ca^{2+} concentration [38]. Our group of previously revealed ventral forebrain-specific HB-EGF KO mice were impaired by long-term potentiation (LTP) induced by a high-frequency stimulation in hippocampus CA1 neurons using slice preparations [66]. HB-EGF KO mice also showed reduction in the activities of CaMKII and GluR1 [66]. CaMKII has been implicated as a key molecule in the induction of LTP [67]. Phosphorylation of AMPA receptors by CaMKII is reported to be particularly important for LTP induction [68,69]. The efficiency of neuronal transmission, known as synaptic plasticity, forms the cellular basis for learning and memory. HB-EGF KO mice were impaired in spatial memory in the Morris water maze and in fear learning in a passive avoidance test [66]. These reports suggest that HB-EGF plays a significant, but yet to be fully identified, role in synaptic plasticity and memory formation.

Here, it is worth noting that neurotrophic factors and cytokines display profound neuromodulatory functions and are involved in the survival and homeostatic maintenance of the central nervous system through regulation of each other's expression. Disruption of the neurotrophin balance has been associated with the pathogenesis of various neurological diseases, such as schizophrenia, amyotrophic lateral sclerosis, and Alzheimer's disease [70–72]. Region-specific HB-EGF deletion altered the levels of various neurotrophic factors in several brain regions in HB-EGF KO mice. In particular, nerve growth factor, neurotrophin-3 (NT-3), or brain-derived neurotrophic factor (BDNF) levels were upregulated in the hippocampus and/or cortex of HB-EGF KO mice, compared with WT mice [66]. Because HB-EGF itself has a neurotrophic effect, the absence of HB-EGF may secondarily alter the expression of neurotrophins. Taken together, these findings suggest that the induction of these growth factors compensates for the deficit in HB-EGF and that the imbalance of neurotrophic and growth factors might partly associate with impaired memory function and synaptic plasticity in HB-EGF KO mice. On the other hand, there are no significant differences between controls and HB-EGF KO mice regarding the relative expression of other EGF family growth

factors, such as EGF, TGF-α, and betacelulin in the prefrontal cortex, using real-time PCR [51].

On the other hand, EGF also promoted the hippocampal LTP in rat [63,73]. Furthermore, EGF and TGF-α increased the paired pulse ration, which represents a reduction in local inhibitory strength [74]. Meanwhile, EGF treatment also diminished the amplitude of excitatory postsynaptic currents in the GABAergic neurons [74]. Given all these reports, EGF and TGF-α, as well as HB-EGF, may be important for the synaptic plasticity and neuronal transmission in the hippocampus.

Roles of HB-EGF in Ischemia-Induced Brain Damage

Neurotrophic and growth factors, such as EGF [75], fibroblast growth factor-2 (FGF-2) [75,76], and BDNF [77] have been implicated in neurogenesis as well as in *in vivo* neuroprotection. For this reason, recent studies have focused on the ability of these factors to promote endogenous neurogenesis as a novel therapeutic strategy against ischemic stroke [78,79]. Focused on HB-EGF, intraventricular injection of HB-EGF into rats also reduced infarct size after focal cerebral ischemia [80]. We recently reported that ventral forebrain-specific HB-EGF KO mice show exacerbated ischemia and reperfusion injury [81]. Similarly, EGF family growth factors, such as EGF and TGF-α, have also been reported to exert protective effects in rodent models of ischemic brain injury [36,82,83]. The level of HB-EGF mRNA in the cortex and hippocampus was increased after cerebral ischemia and reperfusion injury in a time-dependent manner [81,84]. On the other hand, members of the EGF family are differentially expressed and regulated after ischemic brain injury. The time course changes after cerebral ischemia for other major EGF receptor ligands, such as EGF and TGF-α, were investigated, but no changes in EGF mRNA expression were detected, while TGF-α mRNA was increased only at 24 h after middle cerebral artery occlusion (MCAO) and reperfusion [81].

Many studies have shown that acute central nervous system insults, such as seizure, oxidative damage, lesion, traumatic injury, and global and focal ischemia, significantly increase progenitor cell proliferation in the adult brain [85–88]. These newly proliferated cells migrate to the damaged areas of the brain, particularly following cerebral ischemia [89–92]. The major function of neurogenesis in the adult brain seems to generate replacements for the neurons that die regularly in certain brain areas. In normal adult rats, the intracerebroventricular administration of HB-EGF increased bromodeoxyuridine (BrdU)-positive cells in the subventricular zone and in the subgranular zone of the dentate gyrus [80]. HB-EGF stimulates neurogenesis in mouse cerebral cortical cultures *in vitro* [65]. Furthermore, adenovirus-mediated gene transfer of HB-EGF promoted neurogenesis and angiogenesis in the striatum after focal ischemia [93]. Similarly, fewer BrdU positive cells were found in the subventricular zone in HB-EGF KO mice after focal cerebral ischemia [81]. HB-EGF is also associated with ischemia and reperfusion injury in various organs other than the brain, such as the intestine and kidney [94–97]. Similarly, HB-EGF expression was also upregulated after intestinal and renal ischemia and reperfusion injuries [95,98].

The activation of the apoptotic pathway following cerebral ischemia and reperfusion is one of the major processes that lead to cell death [99,100]. Generation of excessive reactive oxygen species (ROS) during reperfusion is known to play a pivotal role in brain injury associated with stroke. These free radicals cause oxidative damage to brain lipids, proteins, and DNA, leading to brain dysfunction and cell death [101]. In the KO mice study for HB-EGF, the numbers of 8-hydroxy-2′-deoxyguanosine (8-OHdG)-positive cells were significantly increased in the cortex of HB-EGF KO mice compared with the WT mice [81]. Previous studies have also shown that HB-EGF decreases both *in vitro* and *in vivo* production of oxygen free radicals [102]. Conversely, oxidative stress increases gene expression of HB-EGF in various types of cells [103,104]. Therefore, HB-EGF may exert its protective role at least in part by preventing oxidation of DNA by the ROS, which increases after transient ischemia.

Taken together, the recent studies indicate that HB-EGF may play a pivotal role in reducing ischemia and reperfusion injury. Endogenously synthesized HB-EGF would appear to exert a neuroprotective effect and also modify the neurogenesis after ischemic brain injury.

Roles of HB-EGF in Nigrostriatal Dopaminergic Neurons

The EGF receptor mRNA was distributed throughout the ventral mesencephalon within cells of the substantia nigra pars compacta and VTA [44,105]. The expression of EGF receptor in nigral dopaminergic neurons favors the direct actions of EGF receptor ligands on this cell population [106]. Several ligands for ErbB receptors have neurotrophic effects on dopaminergic neurons in *in vivo* and *in vitro* [37,107]. ErbB1 ligands also protect the dopaminergic neurons from neurotoxin-induced degeneration and promote the morphological and biochemical differentiation of immature dopaminergic neurons [108,109]. Indeed, mice lacking an ErbB1 ligand and ErbB1-deficient midbrain cell cultures show abnormalities in the development of dopaminergic neurons [107,110]. HB-EGF also enhances the survival of midbrain dopaminergic neurons by activation of the MAPK and the Akt signal pathway [37]. Furthermore, intracerebral administration of recombinant human HB-EGF protects the nigrostriatal dopaminergic system in 6-hydroxydopamine (6-OHDA)-induced rat Parkinson's disease model [109]. HB-EGF and EGF, as well as GDNF, enhance dopamine uptake in mesencephalic cultures [107]. On the other hand, among various neurotransmitters examined, such as dopamine, 5-HT, acetylcholine, and glutamate, only dopamine triggered the release of EGF from neuron-enriched striatal cultures, but not HB-EGF or TGF-α [111].

Dopamine receptors belong to the G protein-coupled receptor superfamily and can activate matrix metalloproteinases (MMPs) and ADAMs, which are responsible for ectodomain shedding [112,113]. The cellular mechanism suggests that once dopamine is released and bound to dopamine D1-like receptors on striatal neurons, the activated MMP/ADAM enzymes shed the membrane-anchored EGF precursors and lets soluble EGF be released to dopaminergic afferent terminals and this promotes dopaminergic development or dopamine release [108,114]. But HB-EGF and

TGF-α might be differently regulated in striatal dopaminergic neurons, or these releases would be carried by the MMP/ADAM enzymes uncoupled with dopamine receptors [111].

The degeneration of nigrostriatal dopaminergic neurons is associated with the pathogenesis of some kinds of neurodegenerative disease, such as Parkinson's disease [115]. A previous study that investigated the EGF family expression in Parkinson's disease revealed protein levels of EGF and tyrosine hydroxylase were decreased in the prefrontal cortex and striatum of patients [108]. On the other hand, HB-EGF or TGF-α levels were not significantly altered in either region of patients [108]. The expression of EGF receptors, such as ErbB1 and ErbB2, were also down-regulated significantly in the striatum and prefrontal cortex of patients, but not other EGF receptors, such as ErbB3 or ErbB4 [108].

These findings suggest that EGF receptor ligands, such as HB-EGF, EGF, and TGF-α, affect the development and function of nigrostriatal dopaminergic neurons, and further studies using KO mice would elucidate potential effects of HB-EGF on these neurons.

Conclusion

As described in this review, a number of studies indicate that HB-EGF would be an important trophic factor in the developing central nervous system and a contributor for higher brain functions. HB-EGF is widely expressed in the central nervous system, including the hippocampus and cerebral cortex, and exerts significant action on the developing and adult nervous system. (1) HB-EGF signaling may play a pivotal role in psychomotor behavior and neuronal transmission, and alterations affecting HB-EGF signaling could comprise a contributing factor in psychiatric disorders. (2) HB-EGF would be important for the synaptic plasticity and neuronal transmission in the hippocampus. (3) HB-EGF, as well as other EGF receptor ligands, affects the development and function of nigrostriatal dopaminergic neurons. (4) Endogenously synthesized HB-EGF would appear to exert a neuroprotective effect and also modify the neurogenesis after ischemic brain injury.

Although some action of HB-EGF overlaps with other ErbB1 ligands, such as EGF and TGF-α, much higher expression of HB-EGF within the brain suggests that HB-EGF serves as a major physiologic ligand for the EGF receptor (ErbB1) within the central nervous system. HB-EGF plays essential roles in the central nervous system. Furthermore, HB-EGF and careful regulation of its activity will be strong targets for treating a number of neurological diseases of the central nervous system.

Conflict of Interest

The authors declare no conflict of interest.

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