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Mini Review

Adult hippocampal neurogenesis and related neurotrophic factors

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New neurons are continually generated in the subgranular zone of the dentate gyrus and in the subventricular zone of the lateral ventricles of the adult brain. These neurons proliferate, differentiate, and become integrated into neuronal circuits, but how they are involved in brain function remains unknown. A deficit of adult hippocampal neurogenesis leads to defective spatial learning and memory, and the hippocampi in neuropsychiatric diseases show altered neurogenic patterns. Adult hippocampal neurogenesis is not only affected by external stimuli but also regulated by internal growth factors including BDNF, VEGF and IGF-1. These factors are implicated in a broad spectrum of pathophysiological changes in the human brain. Elucidation of the roles of such neurotropic factors should provide insight into how adult hippocampal neurogenesis is related to psychiatric disease and synaptic plasticity. [BMB reports 2009; 42(5): 239-244]

The generation of new neurons in the mammalian brain

Over the last decade, many fascinating studies have shown that new neurons are actively generated in two specific regions, the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus of the mammalian brain (1, 2). But why neurogenesis is limited to these two specific regions in the brain is unknown. These findings were obtained as a result of the development of molecular techniques using incorporation of nucleotide analogs (3, 4), viral infection (5), and genetic manipulation (6). Adult neural stem cells in the SVZ migrate through the rostral migratory stream (RMS) into the olfactory bulb where they differentiate into multiple types of interneurons releasing neurotransmitters to mitral or tufts cells (7). Proliferating cells in the SGZ of the dentate gyrus differentiate into immature neurons and are incorporated into the molecular layer, extending axons to the hilus and CA3 regions following the mossy fiber pathway, and projecting dendrites towards the molecular layer to receive signals from the entorhinal cortex (7). These neurons express specific cell surface markers spatiotemporally depending on their maturity and microenvironment (8). The pluripotent neurons from the SVZ and SGZ seem to play different roles and to be regulated by distinct mechanisms (9). By investigating the factors modulating adult neurogenesis, neuronal activity, environmental factors, and psychotropic drugs have been shown to dynamically regulate adult neurogenesis (10). Adult hippocampal neurogenesis is downregulated by stress (11), aging (12), glucocorticoid hormones (12, 13) and drugs of abuse (14), whereas it is upregulated by an enriched environment (3), exercise (15), hippocampal-dependent learning (16), estrogens (17), antidepressant drugs (18, 19), electroconvulsive seizure (ECS) (20), lithium (21), and etc (Fig. 1).

Data regarding the functional significance of adult hippocampal neurogenesis are still conflicting. This may be because the various experiments use different strains, ages of animals, parameters in behavioral tests, and environments. Three aspects of adult hippocampal neurogenesis have been intensively investigated: one is the mechanism of adult neurogenesis, i.e. how new-born neurons proliferate, differentiate,

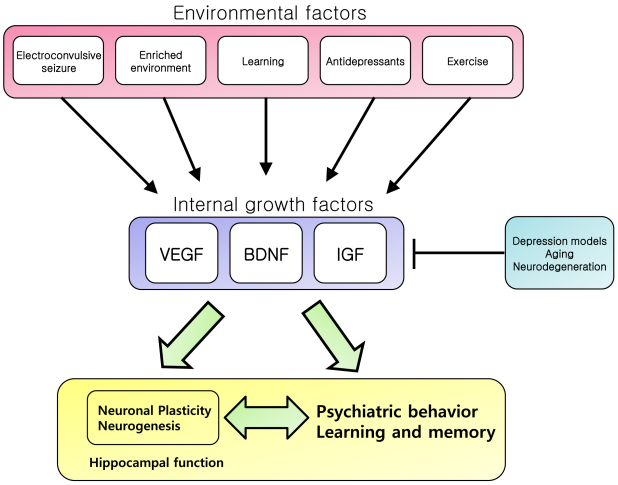

Fig. 1. Signals regulating adult hippocampal neurogenesis.

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and become integrated into neuronal circuits. Another is hippocampal function related to learning and memory: are new neurons required for learning and memory, or do learning and memory increase adult hippocampal neurogenesis? The last aspect concerns the pathophysiological etiology of psychiatric diseases such as depression and bipolar disorder. The mechanism of adult hippocampal neurogenesis *per se* is being actively investigated by the groups of Gage and Song using electrophysiological approaches and genetic manipulation. Here, we will briefly review adult hippocampal neurogenesis in relation to hippocampal function, learning and memory and the modulation of emotion, by considering the neurotropic factors that affect adult hippocampal neurogenesis.

The hippocampus is differentiated along its length, the dorsal part being involved in learning and memory and the ventral part being associated with emotionality (22). This topological difference is linked to different functions: The ventral hippocampus receives inputs from the rostromedial entorhinal cortex, and provides output projections to the prefrontal cortex, amygdale, and nucleus accumbens. On the other hand, the dorsal hippocampus receives input signals from the lateral and caudomedial entorhinal cortex, and has efferents to the dorsal lateral septum and mammillary complex. The two regions also display distinct patterns of gene expression, supporting the differential functional involvement of the hippocampus along its axis (23).

Adult hippocampal neurogenesis and learning and memory

As adult hippocampal neurogenesis was found to occur continuously throughout life, investigators tried to discover the function of the newly generated brain neurons. It has been speculated that newborn cells are required for normal hippocampal function, as suggested by postmortem analysis showing reduced hippocampal volume in patients suffering from stress-related illnesses and depression (24-27). The effect of antidepressant drugs seemed to be blocked by X-ray irradiation that destroyed new-born cells, suggesting that hippocampal neurogenesis mediates the behavioral effects of antidepressant drugs (28). The link between hippocampal neurogenesis and mood disorders also suggested that dysfunction of adult neurogenesis might be the cause of psychiatric illness. This idea is, however, disputed by a series of studies using genetic approaches to specifically target newborn neurons; these demonstrated that adult hippocampal neurogenesis is unlikely to be directly linked to depression but rather to anxiety-related behavior (29). Environmental enrichment does not require hippocampal neurogenesis for its behavioral effect (30). Interestingly, chronic mild stress specifically reduced cell proliferation in the ventral hippocampus, thus connecting hippocampal neurogenesis with the regulatory effect of the ventral hippocampus on emotion (31). Though it does not appear to underlie the etiology of emotional disorder, adult hippocampal neurogenesis is likely to be associated with the regulation of emotion. Does this then mean that an increase in newborn neurons in response to therapeutic drugs or a decrease in their number are only secondary consequences of the treatment or environmental influences? Or do the newborn neurons contribute to the beneficial effect of drugs and to compensating for detrimental effects? Further work to define the mechanism by which antidepressant drugs affect mental disorders should answer this question.

As the hippocampus is the core center for learning and memory, it has been hypothesized that adult hippocampal neurogenesis might participate in hippocampal function related to learning and memory (32). However, the limited evidence and inconsistent results obtained limit our understanding of the link between adult hippocampal neurogenesis and learning and memory. Spatial learning behavior is better in mice strains having more new neurons (33) and reduced production of new neurons due to adverse experience at an early stage is associated with poor learning ability (34, 35), but rats do not have differential strain-dependent learning abilities dependent on adult neurogenesis (36). Even negative regulators of hippocampal neurogenesis sometimes result in enhanced learning (37) and exercise improves learning and memory in aged mice (38), suggesting that the connection between adult hippocampal neurogenesis and hippocampus-dependent learning may not be straightforward. These relationships were studied by ablating newborn cells using the antimitotic agent methylazomethanlol acetate (MAM) and irradiation (16, 39). However a recent study found that specific knock-down of adult neurogenesis impaired spatial and recognition memory in the hippocampus (40). Further work is needed to see if numbers of new neurons are increased by learning or whether new neurons are required for learning and memory (32).

Neurotrophic factors affecting adult hippocampal neurogenesis and psychiatric disorders

Despite the conflicting evidence about the connection between adult hippocampal neurogenesis and emotional impairment, as well as learning and memory, it is certain that several growth factors are involved in the mechanisms regulating adult hippocampal neurogenesis. The involvement of growth factors in the mechanism underlying the effect of antidepressant drugs on hippocampal neurogenesis and antidepressive disorders has been much investigated. Adult hippocampal neurogenesis is positively affected by chronic antidepressant treatment (18), and neurotrophic factors such as BDNF, NGF, and neurotrophin-3 are known to be implicated in adult neurogenesis and neuroplasticity. Among these, BDNF has been intensively studied and shown to be involved in learning and memory, and synaptic plasticity (41). Spatial learning and memory is defective in a BNDF-deficient animal model (42), and overexpression of BDNF causes both anxiogenic and antidepressant behavior (43). BDNF is implicated in the patho-

genesis of depression and the therapeutic mechanism of antidepressants (44, 45). Moreover antidepressant drugs including selective serotonin reuptake inhibitors (SSRI), selective norepinephrine reuptake inhibitors (SNI), and monoamine oxidase inhibitors (MAOI), enhance BDNF expression in the hippocampus (46) and BDNF is downregulated by stress in the hippocampus (47). However, inhibition of BDNF signaling doesn't block the antidepressant-induced neurogenesis (48). Rather, BDNF is likely to be required for a long term survival of newborn hippocampal neurons (48). A polymorphism at 66th amino acid of BDNF coding region is associated with depression as well as other disorders including anxiety and obsessive-compulsive disorder (49). Interestingly, BDNF is epigenetically modified by traumatic stress and drug treatment. BDNF gene transcription is suppressed by DNA methylation, and this is reversed by histone acethylase which is restored by antidepressant drugs (50). NT3 deficiency caused defects both in differentiation of neuronal precursor cells and in spatial learning tasks (51), while NT3 increased the expression of BDNF (52) and modulated BDNF-induced signaling in differentiating hippocampal neurons (53). Also, NT3 was downregulated with NGF by exposure to chronic stress (54).

Insulin-like growth factor-1 (IGF-1), which is primarily produced in the liver and stimulated by growth hormone, plays an important role in cell growth and development. It upregulates neurogenesis in the adult hippocampus (55). It also increases spontaneous firing, increases sensitivity to afferent stimulation, and promotes the generation of newborn cells, all effects on the brain similar to those of exercise, implying that IGF-1 mediates the effect of exercise (56, 57). In addition, expression of IGF-1 is increased by chronic treatment with antidepressant drugs (58) and injection of IGF-1 elicits the same antidepressant behavior as BDNF, suggesting a role in mediating the effects of antidepressant drugs (59).

Vascular endothelial growth factor (VEGF) is a well known growth factor and an important signaling molecule involved in vasculogenesis and angiogenesis (60, 61). It stimulates the production of newborn neurons in vitro and in vivo (62), and a dominant-negative form of VEGF receptor 2 (flk-1) blocked cell proliferation (63). Proliferating cells are closely associated with the vasculature, which indicates that factors released from blood vessels may have a direct impact on adult neural progenitors and that the microenvironment may control the local remodeling of given brain regions (64). Chronic antidepressant drugs induce increased VEGF expression in the hippocampus (65) and VEGF is required for cell proliferation in response to antidepressant drugs (66). VEGF has been identified as one of products upregulated by electroconvulsive seizure, a treatment for depression (65, 67). In addition, exogenous VEGF treatment promotes neurite outgrowth through flk-1, which signals via the MAPK pathway (68). Interestingly, VEGF is required for increased neurogenesis in adult mice exposed to an enriched environment and to exercise (63, 69), which are reported to stimulate adult hippocampal neurogenesis and have an antidepressive effect. Chronic stress, which caused reduced hippocampal neurogenesis, significantly decreased the expression of VEGF and flk-1 in the granular cell layer (70). Taken together, these findings suggest that VEGF plays an important role in the complex pathways by which diverse environmental stimuli affect behavioral outcomes, and may be a strong candidate as a therapeutic target in depression (71).

Erythropoietin (EPO) is a cytokine well known to play a role in inducing erythropoiesis under hypoxic conditions. It also increases adult hippocampal neurogenesis (72, 73). The brains of EPO receptor (EPOR) knockout mice show enhanced apoptosis and the mice are highly sensitive to hypoxia (74), but it is not known if this sensitivity is because EPO has a neuroprotective effect or is a secondary effect of decreased oxygen delivery to the brain. A recent study demonstrates that EPO treatment improves hippocampal-dependent memory by modulating neuronal plasticity and synaptic connectivity, suggesting EPO to be a potential neuropsychiatric drug (75). Image analysis in clinical research has shown that EPO rapidly improves mood and modulates cognitive neural processing, as do serotonergic antidepressant drugs (59). Also, EPO expression is enhanced by electroconvulsive seizure, and EPO induces antidepressant-like behavior (76). BDNF is reported to be increased by treatment with EPO (77) and expression of other molecules implicated in antidepressant action is also increased (76). EOP also prevented the development of global brain atrophy in a mouse model of chronic neurodegeneration (78, 79), and promotes neurite outgrowth and axonal regeneration (80). Interestingly, EPOR expression is increased in schizophrenia and Alzheimer's disease (81).

Closing remarks

There have been many studies of the possible link between the production of new neurons in the adult hippocampus and hippocampal functions such as learning and memory and emotional modulation, though a huge area remains to be explored. Adult hippocampal neurogenesis is an intriguing field because it is immediately altered by subtle changes in the levels of neuronal growth hormones and factors, suggesting that it could be a good indicator of the internal condition of the brain. This, in turn, implies that adult hippocampal neurogenesis may be useful for investigating therapeutic drugs to correct or improve brain function. It is not yet completely understood how the production and maturation of newborn neurons are modulated, and how they interact with mature neurons in a circuit. However, given that the generation of new neurons is affected by modulators secreted by mature neurons, we should not ignore the question of how mature neurons are affected by environmental factors and internal growth factors and eventually modify the pattern of adult hippocampal neurogenesis. To better understand the relationship between adult hippocampal neurogenesis and mature neurons we also need to see how mature neurons respond to trophic factors that are affected by

synaptic plasticity, external factors, and synaptic connections. Study of the role of neurotrophic factors in adult hippocampal neurogenesis may provide insight into the modulation of brain function associated with psychiatric disorders including schizophrenia.

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